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SURGERY

VOL. 40 DECEMBER, 1956 NO. 6

Original Communications

JOINT PARACENTESIS FROM AN ANATOMIC POINT OF VIEW

I. SHOULDER, ELBOW, WRIST, AND HAND

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(From the Department of Anatomy, Emory University)

INTRODUCTION

IN EARLIER years joint paracentesis was performed largely to aspirate either serous or suppurative fluids. With the discovery that locally injected hydrocortisone has beneficial effects on arthritic joints (Hollander and associates[6]), more and more physicians are utilizing this method of treating joint conditions. Although several approaches have been developed for each of the most commonly injected joints (Albee,[1] Kling,[8] Mawson,[9] Speed and Smith,[15] Hollander,[3-5] Sperling,[16] and references cited), to date no anatomical studies have been reported with this problem specifically in mind. Accordingly, at the suggestion of Dr. Arthur M. Pruce, studies were undertaken, the findings of which were presented in demonstration at the 1955 meetings of the American Medical Association. The injection techniques resulting from these studies are being reported elsewhere (Pruce, Miller, and Berger[13]). The present report and that which follows (Miller[10]) constitute companion papers with more extensive analyses of the anatomic reasons for selecting the recommended injection sites.

PRINCIPLES FOR SELECTING SITES FOR PARACENTESIS

In the course of the study the following six principles were developed for selecting and evaluating possible sites:

1. *The Selection of Sites as Far Removed as Possible From Large Nerves, Blood Vessels, or Tendons.*—Flexor surfaces of articulations are generally to be avoided since the major nerves, vessels, and tendons are usually concentrated there. Certain sites on extensor surfaces also should be avoided for this reason;

Aided by grants from the Arthritis and Rheumatism Foundation and Emory University.
Reported in abstract (Miller, Pruce, and Berger[11]).
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for example, the anatomical snuffbox (containing radial artery, superficial radial nerve, cephalic vein) and region of the medial epicondyle (ulnar nerve and superior ulnar collateral artery).

2. *The Use of Bony Landmarks.*—Since both absolute size and proportions vary greatly between individuals of the same racial background, and even more strikingly in individuals of different races, techniques based on absolute measurements are assured of a large element of unreliability. Accordingly, no measurements are offered in this study. On the other hand, the size and position of each anatomical structure are closely related to that of adjacent structures. For this reason, if some prominent anatomical landmark is available in the immediate vicinity, the problem of arriving at the exact location of a target area is greatly simplified. Accordingly, landmarks as close to the injection site as possible were selected. Since bony prominences are more readily palpable, are more constant, and are more closely related anatomically to the articulations than are any other structure, they were selected in each case as points of reference.

3. *Enlargement of the Target Area.*—This may be produced by two means:

A. *Distraction:* (This proved to be most effective in the shoulder, wrist, and metacarpophalangeal articulations.) Where joint capsules are sufficiently loose to permit, the joint surfaces can be separated by distraction. This procedure is to be recommended both because it increases the target area and also because it reduces greatly the hazard of scoring the articular cartilages with the needle tip (see below).

B. *Positioning:* In other cases because of the shapes of the articulating surfaces, enlargement of the target area can be achieved by positioning. The outstanding example of this is the knee. Because of the shapes of the femoral condyles, the vertical extent of the joint cavity is largest when the knee is flexed maximally. Likewise, in the case of the first carpometacarpal articulation, the lateral portion of the joint cavity can be greatly enlarged by adduction because of the saddle-shape of the articulating surfaces.

4. *The Use of Positioning to Increase the Ease of Palpation.*—This proved to be feasible in several instances. For example, it was found that medial rotation of the thigh greatly facilitated palpation of the greater trochanter of the femur by moving it out from under gluteus maximus. In the case of the head of the radius, palpation proved to be facilitated by extension of the forearm since in the extended position the capitulum of the humerus cannot be felt and the head of the radius can be easily distinguished from the lateral epicondyle.

5. *The Use of Positioning to Stretch the Joint Capsule and Its Supporting Ligaments.*—By placing these tough fibrous structures on stretch, entry of the needle tip into the synovial cavities is facilitated. For this reason, in all instances the final positioning of the appendage was planned with this end in view.

6. *Scoring of the Articular Cartilages Is to Be Avoided If at All Possible.*—Hyaline cartilage regenerates poorly, and, particularly in cases in which reinjections are necessary, damage to the contact surfaces may produce conditions

as serious as those being treated. In the case of the knee it is believed that the recommended technique through the patellar tendon completely eliminates this hazard.

ANATOMIC RATIONALE FOR APPROACHES

Specific directions for injections are given in another place (Pruce, Miller, and Berger,[13]); the present report is limited to anatomic studies upon which the recommended procedures are based.

A. *Shoulder Region.*—Bony landmarks selected were: (1) anterior tip of the acromion, (2) angle of the acromion (Figs. 1 and 2). The two most readily palpable bony prominences in the shoulder region are the anterior tip and the angle of the acromion. Since there is a hiatus between the acromial origins of the trapezius and deltoid, the upper central portion of the acromion is subcutaneous and therefore very readily palpable. The anterior tip and the angle are covered by fibers of the deltoid, but these are few in number and do not interfere appreciably in palpation.

Subacromial bursa: The anterior tip of the acromion forms the most superior part of the fibro-osseus "hat" for the head of the humerus (formed by the acromion and the coracoacromial ligament). Immediately subjacent is the subacromial (subdeltoid) bursa. Accordingly, the anterior tip of the acromion constitutes an ideal bony landmark to serve as a guide for the injection of this commonly afflicted bursa. With the arm distracted downward to increase the separation between the bursa and the capsule of the shoulder joint, a needle will enter the bursa if it is passed immediately inferior to the anterior tip. The lateral rather than an anterior approach is recommended in order to avoid the cephalic vein and the deltoid branch of the thoracoacromial artery which lie in the deltopectoral triangle. This approach differs from that of Sperling in the use of distraction and in the use of an angle of insertion (90°) which is more readily estimated than "medial and slightly inferior" (Sperling,[16] p. 120). Both in his and in the Sharp & Dohme brochure[14] it might appear that a slight error in depth of insertion could result in an injection into the scapulohumeral cavity. The lateral approach greatly minimizes this possibility.

Scapulohumeral articulation: The angle of the acromion provides the operator with an ideal bony landmark for injection of the scapulohumeral articulation. Since it overlies posteriorly the contact surfaces between the humeral head and the glenoid fossa, a needle inserted horizontally approximately one fingerbreadth below the angle will pass between the head and the lip of the glenoid fossa (Fig. 2). Internal rotation is recommended to tighten the posterior fibers of the joint capsule. This approach appears to have certain advantages over the anterior approach: (1) To reach the synovial cavity by the anterior approach the needle must pass through the tough tendons of both the coracobrachialis-biceps (shorthead) and the subscapularis. The posterior approach recommended here is through *fleshy* fibers of the deltoid, and infraspinatus. (2) The anterior portion of the capsule is strengthened inferiorly by the coracohumeral and middle glenohumeral ligaments, one or both of which must be pierced in order to enter the joint cavity. By contrast the posterior

Fig 1.—Posterolateral view of shoulder showing angle (*a*) and anterior tip (*t*) of acromion process.

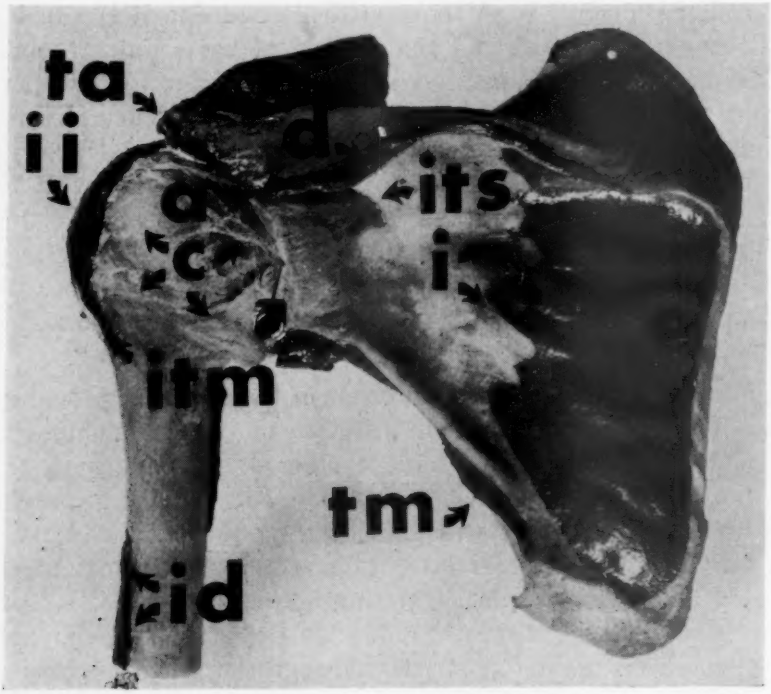

Fig. 2.—Posterior view of right scapula with humerus medially rotated and needle in scapulohumeral joint. Key: *a*, angle of acromion; *c*, capsule of scapulohumeral joint; *d*, deltoid origin; *i*, infraspinatus origin; *ii*, infraspinatus insertion; *id*, insertion of deltoid; *itm*, insertion of teres minor; *its*, inferior transverse scapular ligament; *ta*, tip of acromion; *tm*, teres minor origin.

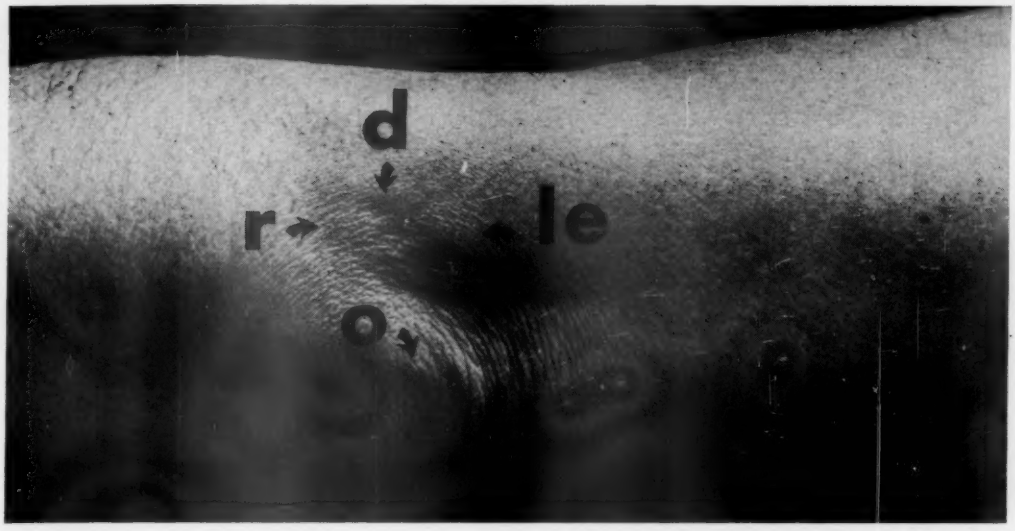

Fig. 3.—Posterolateral view of right elbow showing skin markings. Key: *d*, depression between head of radius and lateral epicondyle; *le*, lateral epicondyle; *o*, proximal tip of olecranon; *r*, head of radius.

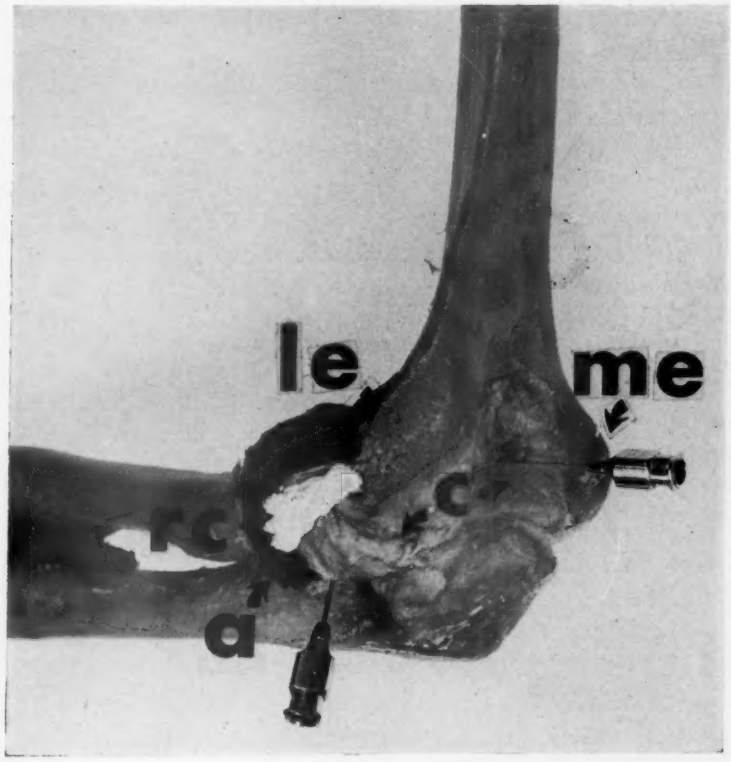

Fig. 4.—Posterolateral view of right elbow with needles in situ for lateral (intra-articular) and posterior (intrasynovial) paracentesis. Key: *a*, annular ligament; *c*, joint capsule; *le*, lateral epicondyle; *me*, medial epicondyle; *rc*, radial collateral ligament. (Upper arrow points to part attached to annular ligament. Lower arrow indicates part which attaches to ulna. Its most distal fibers were removed to expose the underlying fibers of the annular ligament.)

capsule is thin and devoid of strengthening bands. (3) Hollander's injection site is close to the deltopectoral triangle through which courses the cephalic vein. Though very variable in size in this region, it may be a rather large vessel and should be avoided. (4) In addition, certain x-ray films to the contrary not withstanding, the coracoid process lies directly anterior to the glenoid fossa. Since this is true, the writer doubts that the "space between the head of the humerus and the rim of the glenoid cavity" is ever "readily palpable." (Hollander,[5] p. 14). Actually even in a small individual the rim of the glenoid cavity lies about 1¾ inches below the surface and, in addition to being covered by the coracoid superiorly, is overlain by the tendon of the subscapularis and, inferior to the coracoid, by the fused tendons of the coracobrachialis and short-head of the biceps as well as by the anterior fibers of the deltoid muscle.

B. *Elbow Region.*—Paracentesis of the elbow joint medial to the olecranon is not recommended. Since, as it passes posterior to the medial epicondyle, the ulnar nerve (and its accompanying ulnar collateral artery) lies between the skin and the ulnar collateral ligament, it is endangered in any medial approach.

Humeroradial articulation: Since no important vessels or nerves are associated with the lateral epicondyle, a lateral approach to the joint was selected. With the elbow extended, there are three readily palpated bony landmarks on the lateral side (Fig. 3): the lateral epicondyle, the head of the radius, and, between the two, the capitulum of the humerus. Identification of the radial head can be verified by rotation of the forearm. Although flexion of the elbow tends to obscure these landmarks, it is recommended because it draws taut the fibers of the posterior part of the capsule and the radial collateral ligament. If the palpating finger is held against the radial head during this movement, no difficulty is experienced in locating the injection site just proximal to it. The needle should enter from a posterolateral direction and aim toward the largest space in the articulation, the interval between the ulnar and the humeroradial part of the joint (Fig. 4). In this approach the needle attains the joint region by passing through the anconeus muscle.

If the posterior part of the joint cavity is the major site of pathology, entrance may be gained by flexing the elbow and inserting the needle through the triceps midway between the two epicondyles (Fig. 4). Since the synovial membrane encloses the entire olecranon fossa, an intrasynovial injection can be made high enough in the fossa to avoid scoring the articular cartilage.

Olecranon bursa: This bursa, which develops in the subcutaneous connective tissue superficial to the olecranon, does not communicate with the elbow joint. It presents no problems for paracentesis because, when distended, its entire extent is readily observed. If the needle is inserted parallel to the long axis of the ulna, it will follow the long diameter of the ovoid sac.

Region of lateral epicondyle: The lesion in "tennis elbow" commonly involves either the lateral epicondyle, the origin of extensor carpi radialis brevis, its underlying bursa or the radial collateral ligament. (Personal communication from Dr. Paul Reith.) The landmarks selected for this injection were the lateral epicondyle and capitulum. Again palpation is most readily effected

with the arm in extension. For reasons mentioned above, insertion of the needle should be made with the forearm in the flexed position. The needle passes through the extensor carpi radialis brevis. Multiple injections for the area, made by moving the needletip in and out, are recommended in order to disseminate the injected material.

C. *Wrist Region.*—

Radiocarpal articulation: Because of its concentration of nerves, blood vessels and tendons, the flexor surface of this region is inappropriate for joint paracentesis. For the same reason the radial side of the dorsum should be avoided. From lateral mediad the following structures crisscross the region: (1) abductor pollicis longus tendon, (2) extensor pollicis brevis tendon (which forms the radial side of the anatomical snuffbox), (3) radial artery, which in the snuffbox gives off a dorsal carpal branch and the first dorsal metacarpal, (4)

Fig. 5.—Dorsal view of wrist and hand showing needles in position for paracentesis of radiocarpal joint, intercarpal joint, and fifth carpometacarpal joint. Note that the two more proximal needles have been inserted between the tendon of extensor carpi radialis brevis (*ecrb*) and those of extensor digitorum communis (*edc*). The most proximal needle (*RC*) enters the radiocarpal joint through a depression lying immediately distal to Lister's tubercle (*Lt*). The needle in the intercarpal joint (*IC*) has been passed through an even more distinct depression between prominences of the navicular (*n*) and capitate bones. The third needle (*CM*), in the fifth carpometacarpal joint, is placed volar to the insertion of the extensor carpi ulnaris tendon (*ecu*). Key: *CM*, needle in carpometacarpal joint; *ecrb*, groove for extensor carpi radialis brevis tendon; *ecrl*, groove for extensor carpi radialis longus tendon; *ecu*, tendon and groove for extensor carpi ulnaris; *edc*, tendons and groove for extensor digitorum communis; *edq*, tendon and groove for extensor digiti quinti; *IC*, needle in intercarpal articulation; *Lt*, Lister's tubercle; *n*, location of navicular bone (dorsal radial tubercle); *RC*, needle in radiocarpal articulation.

extensor carpi radialis longus tendon, (5) extensor pollicis longus tendon forming the lateral boundary of the snuffbox, and (6) extensor carpi radialis brevis tendon (Fig. 5). Overlying the anatomical snuffbox is, typically, the superficial radial nerve and the main channel of the cephalic vein. The joint is accessible through the tabatière anatomique ("anatomical snuffbox"), but other more favorable sites are available. Although better than the radial, the ulnar side of the wrist has the disadvantage of containing six or seven tendons: the

tendons of extensor indicis, of extensor digitorium communis (3 or 4), of extensor digiti quinti, and of extensor carpi ulnaris. It likewise has a cutaneous nerve (the dorsal branch of the ulnar) and vein (the basilic). Between the

Fig. 6.—Dorsal view of wrist and hand. Depression between tendons of extensor carpi radialis brevis and extensor digitorum communis tendons indicated by arrow. This is recommended site for paracentesis of wrist (p). Key: *ext carp,* extensor carpi radialis brevis; *ext dig,* extensor digitorum communis; *ext dig q,* extensor digiti quinti; *ext pol b,* extensor pollicis brevis; *ext pol l,* extensor pollicis longus; *p,* site for paracentesis.

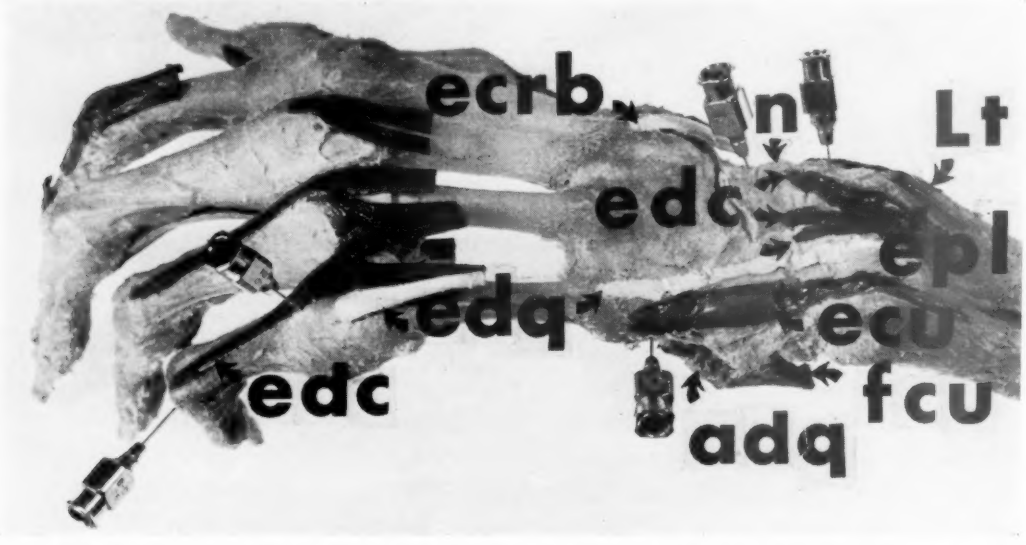

Fig. 7.—Dorsomedial view of wrist and hand showing, in addition to the needles in Fig. 6, needles in the fifth metacarpophalangeal joint and in one interphalangeal joint of the fifth digit. Key: *adq,* origin of abductor digiti quinti; *ecrb,* tendon of extensor carpi radialis brevis; *ecu,* tendon of extensor carpi ulnaris; *edc,* grooves or tendon of extensor digiti communis; *edq,* tendon and groove of extensor digiti quinti; *epl,* groove for extensor pollicis longus; *fcu,* tendon of flexor carpi ulnaris; *Lt,* Lister's tubercle (dorsal radial tubercle); *n,* location of the navicular bone.

structures of the anatomical snuffbox and the common extensor tendons is a space containing no large nerves, blood vessels, or tendons and marked by a bony landmark, the dorsal radial tubercle (of Lister). This bony eminence near the distal end of the radius is located between the grooves for the extensor carpi radialis brevis and extensor pollicis longus. When the wrist is extended against resistance, a depression may be seen distal and slightly ulnar to Lister's tubercle (Fig. 6). This is the site of choice for paracentesis of the radiocarpal joint (Figs. 5 and 6).

Flexion and ulnar deviation of the hand opens the joint cavity dorsally and also stretches the capsule and dorsal radiocarpal ligament. Distraction of the hand may further increase the joint space.

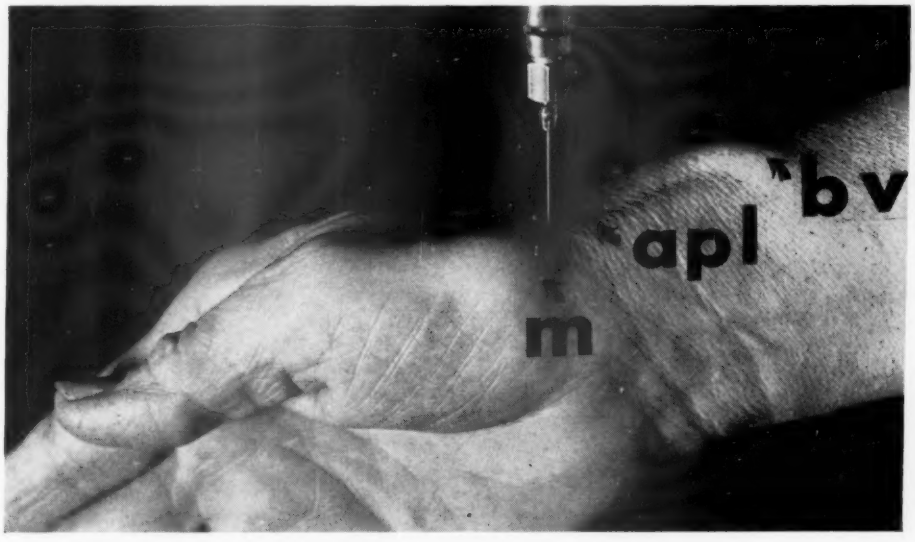

Fig. 8.—Site for paracentesis of first carpometacarpal articulation. With thumb adducted the base of the first metacarpal is accentuated. Needle enters the joint cavity immediately volar to the tendon of insertion of abductor pollicis longus (*apl*). Key: *apl*, fold produced by abductor pollicis longus; *bv*, basilic vein; *m*, base of first metacarpal.

Intercarpal articulations: Since the joint cavities of these articulations usually communicate freely, a single injection site usually is adequate. Lister's tubercle should be palpated and, with the patient clenching the fist, the finger is placed between the tendons of extensor carpi radialis brevis and extensor digitorum communis. As the wrist is being flexed, the dorsum of the navicular bone becomes palpable, and distal to it a depression between it and the capitate. Material injected here (Figs. 6 and 7) usually will pass to all the intercarpal cavities (excepting the pisiform) and, in addition, the middle three carpometacarpal joint spaces.

D. *Carpometacarpal Articulations.*—

1. *Of the thumb:* Since the articular facet on the greater multangular is saddle-shaped, adduction of the thumb opens the radial side of the articulation. This has three effects which facilitate paracentesis. (1) It aids in locating the base of the metacarpal. (2) It increases the target area. (3) It stretches the

strong but loose capsule and its internal strengthening band, named by Haines[2] the "radial carpometacarpal ligament." The approach is anterolateral, with the needle entering just volar to the tendon of abductor pollicis longus (Figs. 8 and 9).

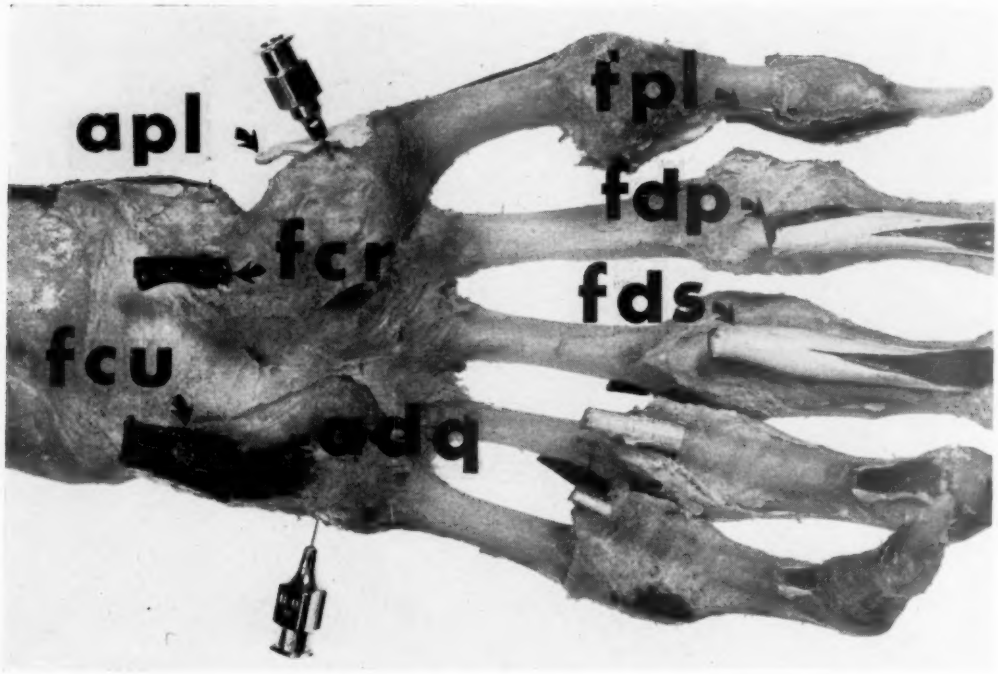

Fig. 9.—Volar aspect of wrist and hand showing needles in situ for carpometacarpal paracentesis. Note: (1) Anterolateral approach for first carpometacarpal joint with needle entering volar to tendon of abductor pollicis longus (*apl*). (2) Medial approach with needle entering dorsal to abductor digiti quinti (*adq*). Key: *adq*, tendon of abductor digiti quinti; *apl*, tendon of abductor pollicis longus; *fcr*, tendon of flexor carpi radialis; *fcu*, tendon of flexor carpi ulnaris; *fdp*, tendon of flexor digitorum profundus; *fds*, tendon of flexor digitorum sublimis; *fpl*, tendon of flexor pollicis longus.

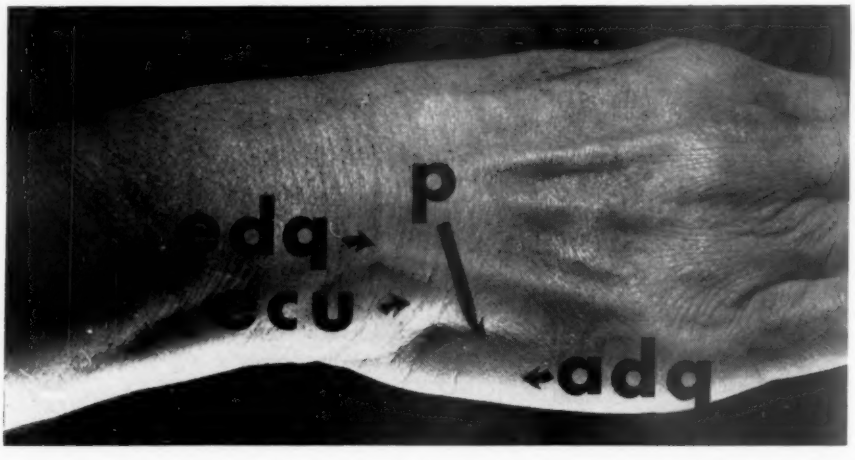

Fig. 10.—Dorsal view of wrist showing landmarks for paracentesis of fifth carpometacarpal joint. Note: Adduction against resistance brings into prominence the tendon of insertion of the extensor carpi ulnaris (*ecu*). Key: *adq*, abductor digiti quinti; *ecu*, tendon of extensor carpi ulnaris; *edq*, tendon of extensor digiti quinti; *p*, site for paracentesis.

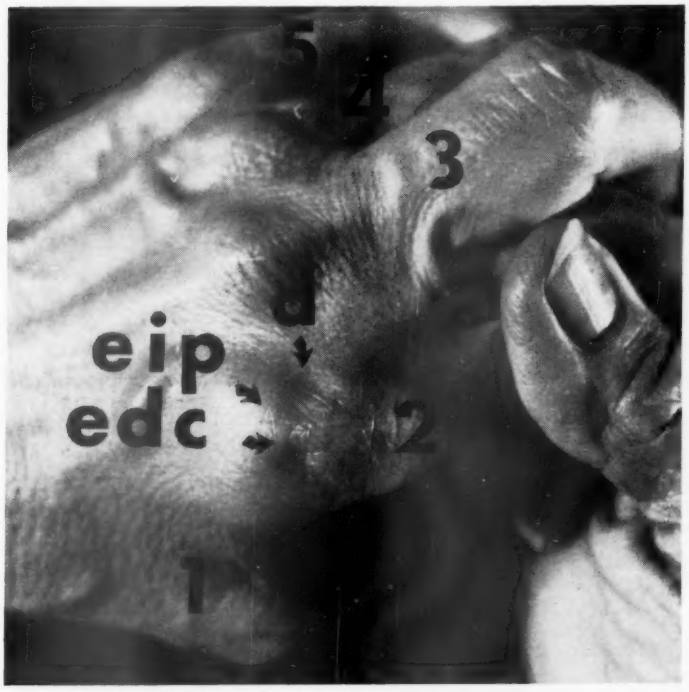

Fig. 11.—Dorsal aspect of hand showing site for injection of second metacarpophalangeal articulation. Note: Distraction of the digit emphasizes the depression medial and lateral to the tendons of insertion of the extensors crossing the joint. Key: *1*, First digit (thumb); *2*, second digit (index); *3*, third digit (middle finger); *4*, fourth digit (ring finger); *5*, fifth digit (little finger); *edc*, tendon of extensor digitorum communis; *eip*, tendon of extensor indicis proprius; *d*, depression which appears upon distraction of the digit (the recommended injection site).

Fig. 12.—Dorsal aspect of hand showing site of injection of fifth metacarpohalangeal articulation. Note: Distraction of the little finger produces a depression on either side of the tendon of the extensors crossing the joint. Key: *3*, third digit (middle finger); *4*, fourth digit (ring finger); *d*, depression which appears upon distraction; *edcq*, tendons of extensor digitorum communis and extensor digiti quinti.

2. *Of the fifth digit:* The carpometacarpal joint of the little finger is readily located for joint paracentesis.

If the patient adducts the hand against resistance, the tendon of extensor carpi ulnaris and its insertion on the head of the fifth metacarpal may be easily palpated (Fig. 10). After abduction to open the joint and stretch the capsule, the needle may be inserted proximal to the base of the metacarpal. It passes between the extensor carpi ulnaris tendon and the abductor digiti quinti muscle (Figs. 9 and 10).

E. *Metacarpophalangeal Articulations.*—As might be expected from their ability to undergo a considerable range of movement, the capsules of these joints are loose. For this reason distraction is an effective means of increasing the target area. This is true particularly in the case of the thumb and little finger, whose range of movement is the greatest. Distraction is least effective in the case of the third and fourth fingers, with the index finger in an intermediate position in this regard. Since the volar and dorsal surfaces are occupied by tendons, and since the collateral ligaments, blood vessels, and nerves lie along the medial and lateral surfaces of the digits, the recommended point for insertion of the needle is on the dorsal surface on either side of the extensor tendons. The recommended bony landmark is the head of the metacarpal with the fingers flexed (Fig. 7). If passively flexed and distracted (Figs. 11 and 12), the separation between metacarpal and first phalanx is accentuated and penetration facilitated.

F. *Interphalangeal Articulations.*—With less range of motion, these joints have tighter capsules than the ones just discussed. Consequently, distraction generally is of little value in increasing the joint space. The bony landmark (the head of the more proximal bone), the site of injection (immediately medial or lateral to the extensor tendon), and the anatomic rationale for this selection is the same as in the case of the metacarpophalangeal joints (Fig. 7).

DISCUSSION

Since joint paracentesis is inherently an extremely simple procedure, there is no fundamental reason why it should not be part of the office treatment of any physician who is willing to restudy the regional anatomy of joints. This fundamental simplicity, however, should not delude one into believing that anatomical facts and principles such as those enumerated earlier can be disregarded with impunity.

Because joints and ligaments are difficult to dissect, the average student at the end of his study of anatomy has seen and knows less about articulations than about any other part of the body. Unless this deficiency is remedied in his subsequent training, it would behoove him to review thoroughly the regional anatomy of each joint before undertaking to treat it. Even in the hands of the most experienced, failure to produce improvement is common in certain injection sites. In other sites, failures are rare. Hollander,[3, 7] emphasizes that therapeutic failures with hydrocortisone injections occur in the same joints in which difficulties are encountered in aspiration. This strongly suggests that failure to penetrate into the joint cavity rather than variability of hormone

preparation or of patient response to the hormone is responsible for the lack of benefit. It suggests further that a reappraisal of injection techniques may result in increases in percentages of successes.

Table 2 of Hollander's report in 1954[7] contains an analysis of the results of 10,179 intrasynovial injections of hydrocortisone using his techniques. Below in tabular form is a comparison of his approaches to the synovia of the superior extremity and those recommended here together with the percentages of failures which he reported.

From Table I it may be noted that, with the exception of the wrist, the largest percentages of failures were using injection sites which were least similar to those recommended from this anatomical study. Those with the smallest percentages of failures (the elbow and phalanges) were achieved by use of very similar sites to those recommended here. Whether and to what extent these observations are correlated could only be determined by extensive clinical trials which are lacking, but on strictly anatomical grounds the suggested approaches would seem to offer certain advantages.

TABLE I. COMPARISON OF RECOMMENDED APPROACHES AND THOSE EMPLOYED BY A GROUP REPORTING 10,197 INJECTIONS OF HYDROCORTISONE

	RECOMMENDED APPROACHES	HOLLANDER ET AL.[7]		
		APPROACHES	NO. INJECTED	PER CENT FAILURE
Shoulder	Posterior (inferior to acromial angle)	Anterior	373	32
Subdeltoid bursa	Lateral (inferior to tip of acromion)	Superolateral) (chronic) (acute)	 221* 82*	 51* 21*
Elbow	Posterolateral (between lateral epicondyle radius and ulna)	Posterolateral (needle parallel to ulna)	382	12
Wrist	Dorsal (distal to Lister's tubercle)	Dorsal (distal to radius, lateral to tabatière)	489	33
Phalanges	Dorsal (medial or lateral to extensor tendons, with distraction)	Dorsal (with distraction)	430	13

*Not listed separately in 1954 report. These figures and percentages are from Table 1, Hollander.[3]

SUMMARY

A study of the anatomy of joints as applied to paracentesis resulted in the enumeration of the following principles for selecting sites: (1) the selection of sites removed from large vessels, nerves, or tendons; (2) the use of bony landmarks; (3) the use of positioning to aid in palpation; (4) the use of distraction and positioning to enlarge the target area; (5) the use of positioning to stretch the capsule; (6) avoidance of scoring articular cartilages.

Using these principles as criteria, the following sites were selected for joint paracentesis:

1. For the subacromial bursa: a lateral approach inferior to the anterior tip of the acromion with the arm distracted.

2. For the shoulder joint: a posterior approach one fingerbreadth below the angle of the acromion, with the arm medially rotated.

3. For the elbow joint: a posterolateral approach proximal to the head of the radius with the elbow flexed.

4. For the region of the lateral epicondyle: a lateral approach with the elbow flexed.

5. For the radiocarpal joint: a dorsal approach in the space just distal to Lister's tubercle between the extensor digitorum communis and extensor carpi radialis brevis tendons, with the wrist flexed and ulnar deviated.

6. For the intercarpal joints: a dorsal approach radial to the common extensor tendons and distal to the lunate with the wrist flexed and ulnar deviated.

7. For the first carpometacarpal joint: an anterolateral approach with the thumb strongly adducted.

8. For the fifth carpometacarpal joint: a medial approach between extensor carpi ulnaris and abductor digiti quinti.

9. For the metacarpophalangeal joints: a dorsal approach on either the radial or ulnar side of the extensor tendon aided by flexion and distraction.

10. For the interphalangeal joints: the same approach as for the metacarpophalangeal joints.

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CHANCES OF FINDING COMPATIBLE TRANSPLANT DONORS

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IT IS well established that the generally observed failure of transplants of tissue from one human being to another to become permanently established is due to immunological reaction on the part of the recipient to hereditary antigens in the tissues of the donor, although it is not always possible to demonstrate circulating antibody. This is shown, for example, by the successful transplantation of tissues from one identical twin to another, and successful transplantation of tissue from incompatible donors to patients with agammaglobulinemia.[2]

The seeming individual specificity of tissues is due not to the presence of any antigen which is unique but to the rarity of identical combinations of the various antigens, individually fairly common, which affect "histocompatibility."[3] The blood-group antigens seem to be among these.

It is of interest to estimate the chances of obtaining a compatible transplant if the donor is selected at random. A preliminary mathematical treatment of this problem has been given by Good,[1] but the treatment offered here is somewhat simpler and, it is believed, based upon somewhat more probable assumptions. In any case, the present estimates are distinctly less optimistic.

Since most of the blood group genetic loci can be occupied by any one of at least two antigen-producing alleles, we may logically suppose that this is true of histocompatibility loci in general. If there are just two alleles, we may represent the frequency in the population of one by p and of the other by 1 – p. Then if donors for transplants are selected at random, we shall have the following situations:

Combination	Antigens in donor	Antigens in recipient	Probability of combination
1	AA	AA	p^4
2	AA	BB	$p^2(1-p)^2$
3	AA	AB	$2p^3(1-p)$
4	BB	AA	$p^2(1-p)^2$
5	BB	BB	$(1-p)^4$
6	BB	AB	$2p(1-p)^3$
7	AB	AA	$2p^3(1-p)$
8	AB	BB	$2p(1-p)^3$
9	AB	AB	$4p^2(1-p)^2$

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Now presumably the recipient will react immunologically to a transplant, and as a result reject it, only in situations 2, 4, 7, and 8, where the donor has an antigen not possessed by the recipient. The other situations, 1, 3, 5, 6, and 9, will be favorable and the transplant will take and become permanent. The combined probabilities of these situations are

$$p^4 + 2p^3(1-p) + (1-p)^4 + 2p(1-p)^3 + 4p^2(1-p)^2 = 2p^4 - 4p^3 + 4p^2 - 2p + 1 \quad [1]$$

This expression has a minimum value of 0.625 when $p = 1 - p = \frac{1}{2}$.

If one of the allelic genes is recessive, the probability of a compatible transplant becomes

$$P = p^4 - p^2 + 1$$

where p is the frequency of the recessive gene. This has a minimum of 0.75 when $p = \sqrt{(0.5)}$ and the frequency of the dominant type equals the frequency of the recessive type = 0.5, as noted by Good.[1]

When more than 2 alleles are present, the formulas become somewhat more complicated. For instance, if we assume that transplants from donors of blood group O are compatible with recipients of any group, but that otherwise the above rule applies, we find the probability that a transplant made at random will be compatible with respect to the ABO blood group system is

$$P = r^2 + (p^2 + 2pr)^2 + (q^2 + 2qr)^2 + 2pq(1 - r^2) \quad [2]$$

where p, q, and r are the frequencies of the genes *A*, *B*, and *O*, respectively. For the population of the United States this gives P = 0.635 approximately.

If n alleles can occupy a locus, we may simplify the calculations by assuming that their frequencies are equal, which in many cases gives results not far from the truth. We easily obtain as the formula for the chances of a compatible transplant

$$P = (4n - 3)/n^3 \quad [3]$$

For three equally frequent alleles, this formula gives P = 0.333, as contrasted with P = 0.625 for two alleles.

If the alleles are not equally frequent, the true probability may be greater than the value given by the above formula, which is a minimum. For instance, for the Kell system, where $k = 0.955$, the true probability is about 0.91, whereas the assumption that the alleles are equally frequent (assuming $k = 0.5$) gives P = 0.625, as did the previous formula.

In the case of the MNS and Rh systems, where a gene (or chromosone) may cause the production of more than one antigen, these simple formulas do not work, but results which are not very much in error may be obtained by assuming the various antigen pairs, as C and c, D and d, and E and e, are inherited independently, applying formula [1] to each pair, and multiplying the results together. For example, if the calculations for the MNS system are made as if the MN and Ss pairs were independent, an estimated

probability of a compatible transplant, for the English or American populations, of 0.411 is obtained, which compares favorably with the correct value of 0.429. Applying this method to the Rh system we obtain P = 0.308.

The chances of getting a transplant compatible with respect to all 9 of the well-studied blood group loci (ABO, MNS, Rh, P, Lutheran, Lewis, Kell, Duffy and Kidd) simultaneously is the product of the separate probabilities, since they are inherited independently (unless Lutheran and Lewis are loosely linked), and turns out to be about 0.0109, or about $\frac{1}{92}$. Thus successful transplants ought to be obtained in about one in 100 random trials. No such percentage of successes is actually observed, however, which we may attribute to (a) the action of other blood group systems which we have not considered, and (b) the action of other histocompatibility antigens. The exact number of other histocompatibility loci in man is unknown, and we can only guess. It seems likely that there are at least 10 additional loci. In order to make the number of loci considered the same as that dealt with by Good,[1] let us take 11 as a probable number. If we assume only 2 equally frequent alleles at each of these, the probability of a transplant compatible for all is $(0.625)^{11}$ or 0.00568. The probability of getting a transplant compatible with respect to the 9 blood group loci and the hypothetical 11 histocompatibility loci simultaneously is

$$0.0109 \times 0.00568 = 0.0000620$$

or about $\frac{1}{16,000}$. This figure is considerably less than the value of $\frac{1}{300}$ arrived at by Good, but the true probability may well be even lower.

It is thus understandable that there seems to be an almost complete individuality of human tissues, and that the chances of finding by a process of trial and error a compatible transplant donor are negligible.

SUMMARY

Formulas are given for the probability of finding a compatible transplant donor. If the 9 major blood group systems alone are considered the chances are shown to be about 1 in 100. Assuming that there are at least 11 other histocompatibility loci involved, the over-all chances are estimated at 1 in 16,000.

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THYMIC TUMOR AND ACQUIRED AGAMMAGLOBULINEMIA: A CLINICAL AND EXPERIMENTAL STUDY OF THE IMMUNE RESPONSE

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THE simultaneous occurrence of acquired agammaglobulinemia and benign thymoma in a human being suggested that the thymus might participate in the control of antibody formation. A brief report of this case and a description of the tumor excised are included in this report. The suggestion, by this case, that this prominent lymphoid organ might play a role in immunologic control mechanisms provoked reflections which seemed compatible with this hypothesis. For example, during the neonatal period, when responsiveness to antigenic stimulation is deficient,[3] the thymus is a relatively prominent organ.[2] In contradistinction to other lymphoid organs, the thymus does not seem to participate in the formation of antibody. Under circumstances where local production of antibody can be demonstrated in lymph nodes and spleen, the thymus does not produce significant antibody.[7] Furthermore, the morphologic expression of active antibody formation, namely, plasmacytosis, does not occur in the thymus in response to even the most intensive antigenic stimulation.[1, 4, 5, 10] The immune response as affected by thymectomy was therefore studied, utilizing a quantitative immunochemical system, and it has been demonstrated in this study that the thymus in young rabbits neither enhances nor inhibits antibody production.

CASE REPORT

F. H., UH 838089, a 55-year-old white laborer, was admitted to the University of Minnesota Hospitals for the first time in June, 1951, with a history of cough, recurrent pneumonia, weakness, and a weight loss of over 40 pounds during the preceding twelve-month period. History revealed that the patient had previously been well and had no trouble from recurrent infection. Roentgen examination of the chest revealed a large mass in the anterior mediastinum (Fig. 1, *A* and *B*). At that time, the total serum protein was 5.1 Gm. per cent; the patient was tuberculin negative. A decision was made to operate upon this patient but recurrent episodes of pneumonia made it necessary to postpone operation for several months. Finally on Nov. 9, 1951, an anterior mediastinal tumor weighing 565 grams was excised and proved, on microscopic examination, to be a benign thymoma (Fig. 2, *A* and *B*). During the subsequent four years, the patient continued to suffer from

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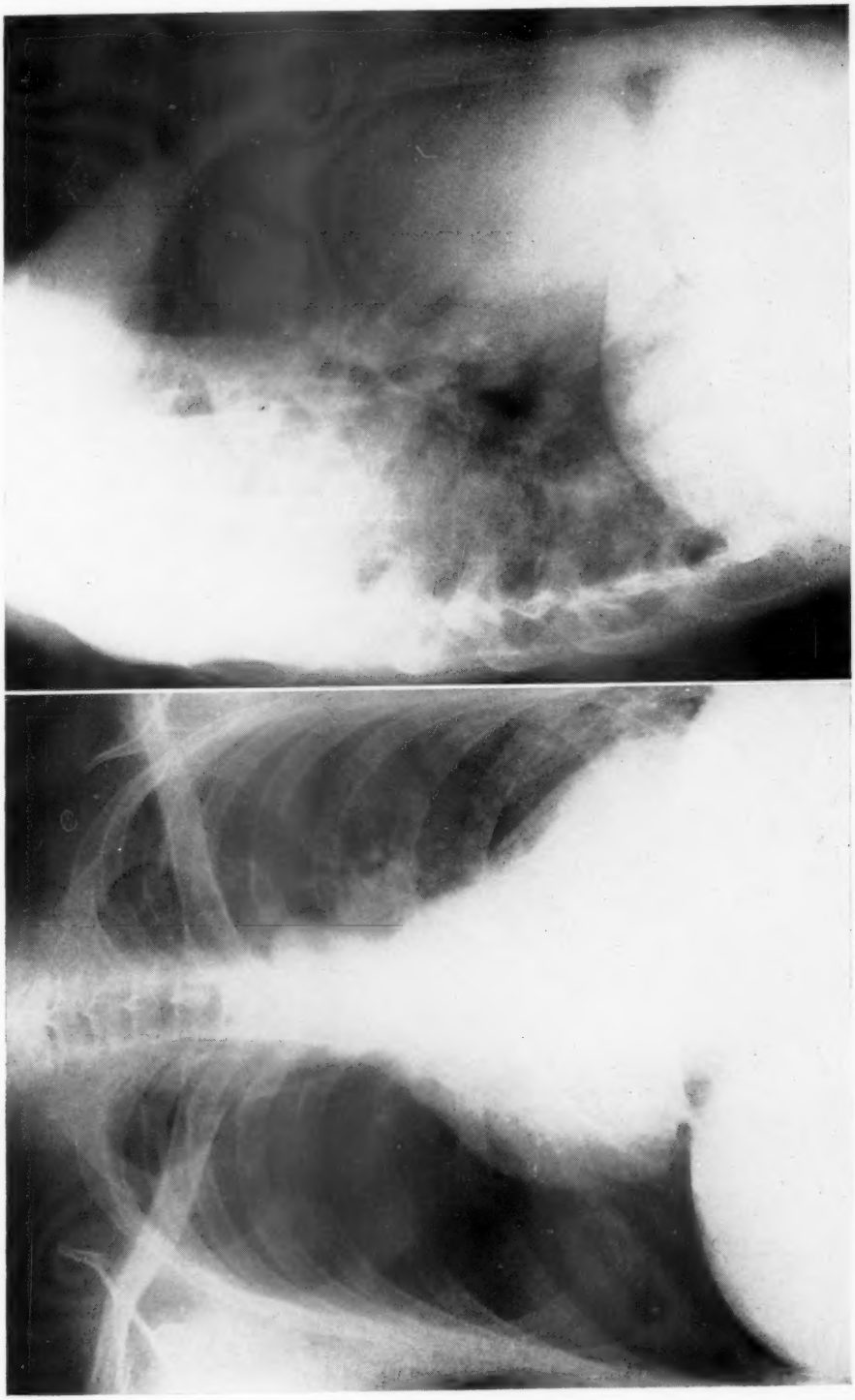
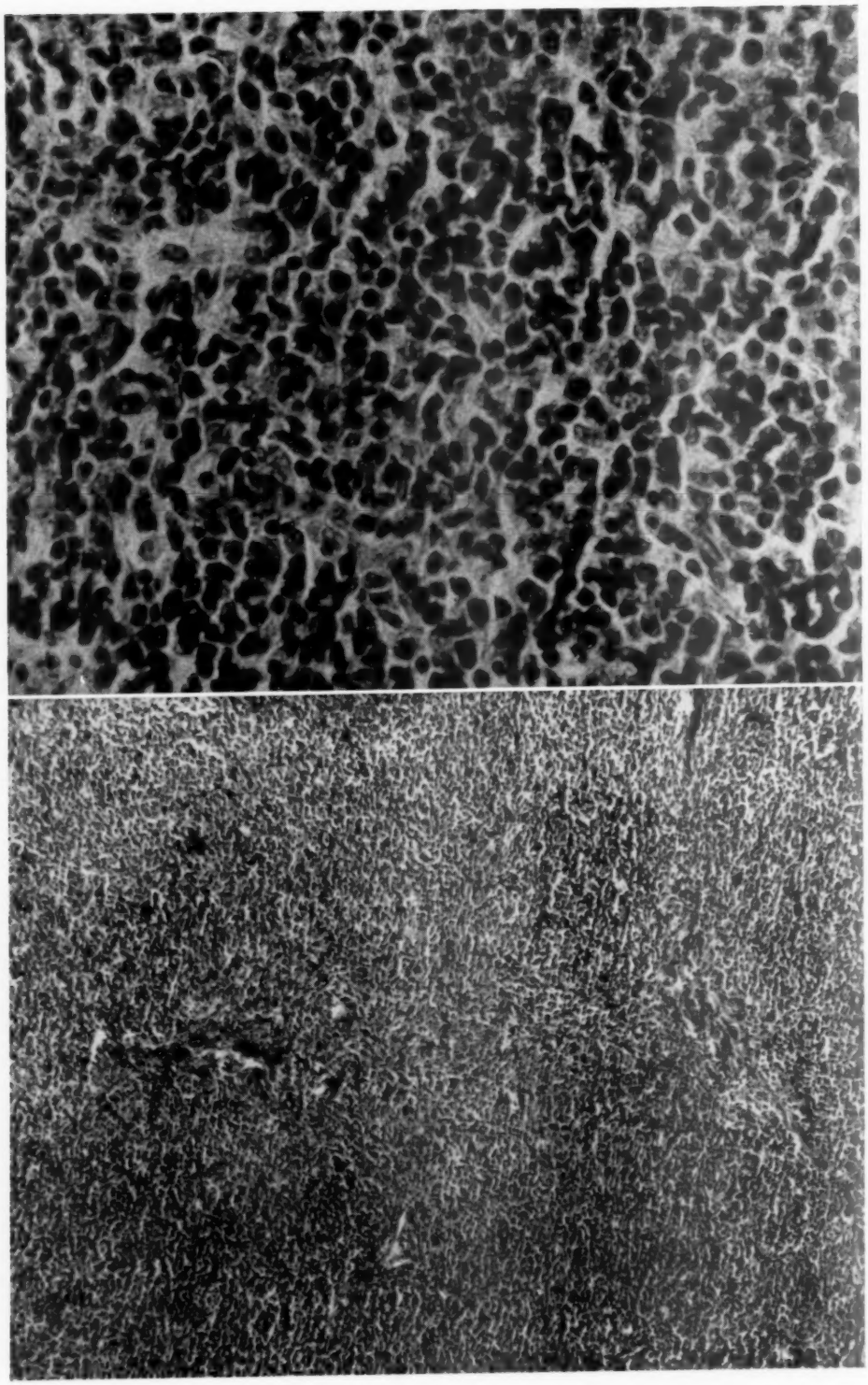


B.

A.

Fig. 1.—Posteroanterior (*A*), and lateral (*B*) roentgenograms showing the thymus tumor which appeared to develop in association with the onset of acquired agammaglobulinemia.



B.

A.

Fig. 2.—Low-power (*A*) and high-power (*B*) microscopic views of the thymus tumor excised from the patient with acquired agammaglobulinemia.

recurrent infection, having at least 17 separate attacks of pneumonia, proved on several occasions to be due to pneumococci, which responded on each occasion to antibiotic therapy. In addition, the patient had recurrent bacterial upper respiratory disease and on several occasions had septicemia. Because of the frequency of these severe infections, he was readmitted to the University Hospitals in April, 1954, for re-evaluation; at this time, the total serum proteins were 5.4 Gm. per cent, with 3.5 Gm. albumin and 1.9 Gm. total globulin. Electrophoretic analysis of the serum showed an absence of gamma globulin, and estimation of the gamma globulin by an immunochemical method showed the serum concentration of the latter to range between 40 and 70 mg. per cent. Normal serum gamma globulin values obtained by this method range from 600 to 1,300 mg. per cent. The bone marrow, lymph nodes, and blood of this patient showed a virtually complete absence of plasma cells.[6] There was also failure of plasma cell development in lymph nodes and bone marrow following intensive antigenic stimulation. The patient was blood group A, and demonstrated very low titers of anti-B antibody in his serum; injection of 2 c.c. of group B cells subcutaneously produced no reaction nor any significant rise in anti-B titers. The patient produced no antibodies upon stimulation with typhoid, paratyphoid, pneumococcal polysaccharide antigens, or diphtheria toxoid. In addition, he failed to respond to a number of potent viral antigens, including mumps, the three polio antigens, several rickettsial antigens, and the antigens of western equine encephalitis. A full-thickness homologous skin graft was applied on June 4, 1954; this graft was accepted and persisted for twelve weeks, but sloughed completely after that time. Skin taken from the agammaglobulinemic patient applied to an immunologically normal person was sloughed 24 days after application. This result represents prolonged survival of the skin homotransplant in the agammaglobulinemic patient. In December, 1954, the patient developed intense jaundice and died on Dec. 25, 1954. Post-mortem examination revealed acute yellow atrophy of the liver. No evidence of malignant disease was found on the autopsy examination. The observation of the associated development of benign thymoma, acquired agammaglobulinemia and immunologic paralysis suggested that the relationship between the thymus gland and antibody production might bear reinvestigation with the postulate in mind that thymic function might tend to inhibit antibody production. After this study was begun another case in which thymoma was associated with the development of acquired agammaglobulinemia has been discovered,[11] lending additional credence to the postulate that thymic activity might be related to immunological responsiveness. To test this postulate the following experiments were performed.

MATERIALS AND METHODS

Twenty-nine hybrid albino rabbits from a single breeding stock, weighing 1,000 to 1,500 grams, were separated randomly into 3 groups. After a fourteen-day acclimatization period in air-conditioned, humidity-controlled quarters on an ad libitum diet of Purina pellets, thymectomy was performed on 7 of the animals. The animals were anesthetized with intravenous Nembutal, the skin shaved, washed with soap, and prepared with tincture of Zephiran 1 per cent. With sterile precautions, thymectomy was performed through a midline anterior cervical incision with upper sternotomy. A pseudocapsule around each lobe of the thymus made it possible to excise the organ completely. Sham operation was carried out in 9 animals on the same day as the thymectomies and consisted of exposure and manipulation but not excision of the thymus. Closure was accomplished with running silk sutures in layers. Fourteen days later, a dose of 30 mg. BSA* in a volume of 2 ml., using sterile isotonic pyrogen-free saline solution as diluent, was given intravenously to all animals. Group I consisted of 7 thymectomized rabbits, group II of 9 rabbits that had sham operations, and group III of 13 controls not operated upon. The animals were bled by cardiac puncture on the ninth, twelfth, nineteenth, and twenty-ninth days following the injection of antigen. The blood was allowed to clot at room temperatures for one hour, placed at 1° C. overnight, the clots rimmed and centrifuged at 2,000 r.p.m. at 1° C., and the serum decanted; the serum was recentrifuged, poured off into sterile tubes, and

*Bovine Plasma Albumin, Armour Laboratories, Lot P67502.

stored at -26° C. until used. Quantitative estimations of antibody content were accomplished approximately eight weeks after processing. At the time of analysis, each serum was clarified by centrifugation at 3,000 r.p.m. for one hour.

The procedure employed for estimation of antibody content of the sera was a modification of the quantitative precipitin determination previously described.[9] This consisted of preliminary determinations utilizing 0.5 ml. aliquots of antisera against 0.5 ml. aliquots of the antigen at dilutions of 1, 3, 6, and 9 mcg. antibody N per ml. After mixing by agitation, the tubes were capped with Parafilm, incubated at 37.5° C. for one hour, and placed in the cold for eight days; the tubes were shaken each day, then centrifuged at 3,000 r.p.m. in the cold for one hour and the supernates quickly poured off and tested for the presence of excess antigen in capillary tubes, with the use of hyperimmune antiserum capable of detecting at least 0.5 mcg. antigen N. The final determinations were performed using 1.0 ml. aliquots of antiserum and antigen; the latter were used in dilutions of increasing concentrations by increments not exceeding 2 mcg. N, as dictated by the preliminary determinations. The tubes were treated as above; the supernates were analyzed for the presence of excess antigen. The precipitates were washed twice with cold nitrogen-free 0.145N NaCl, and the nitrogen content estimated colorimetrically using the Beckman Spectrophotometer at 650 μ. Total precipitate nitrogen was read from a standard curve on a

TABLE I. RELATIONSHIP OF THYMECTOMY TO ANTIBODY PRODUCTION

ANIMAL NO.	MICROGRAMS ANTIBODY N PER MILLILITER SERUM			
	NINTH DAY	TWELFTH DAY	NINETEENTH DAY	TWENTY-NINTH DAY
Group I: Thymectomy.—				
1	0.0	21.65	33.60	15.25
14	0.0	53.00	21.40	8.62
26	0.0	0.00	0.00	4.30
30	0.0	50.00	34.20	16.35
37	0.0	45.90	32.00	9.01
38	0.0	35.58	14.30	9.60
92	- -	0.00	- -	4.30
Mean	0.0	29.45	22.58	9.63
Group II: Sham-operated.—				
28	0.0	7.30	6.25	- -
27	41.0	56.80	38.90	- -
9	0.0	52.80	19.00	10.30
34	5.27	24.83	13.15	11.20
11	0.0	0.00	21.40	8.25
32	0.0	50.30	15.40	4.36
12	0.0	43.20	12.20	10.90
6	0.0	29.50	8.77	4.36
24	0.0	0.00	- -	- -
Mean	5.14	29.41	16.88	8.23
Group III: Nonoperated Controls.—				
35	0.0	5.85	6.70	0.0
22	0.0	43.67	28.50	16.10
7	- -	10.80	- -	- -
33	- -	- -	6.70	0.0
36	0.0	- -	13.38	- -
19	0.0	12.76	7.30	0.0
18	0.0	0.00	12.50	5.20
17	0.0	33.10	11.75	5.20
21	- -	56.00	49.10	29.80
20	21.90	- -	37.50	25.20
16	- -	- -	19.15	- -
8	- -	- -	6.70	0.0
87	- -	- -	- -	5.20
Mean	3.13	23.17	18.12	8.67

sample of purified human gamma.[8] In both preliminary and in final determinations, the individual sera of all three groups of animals were precipitated simultaneously, and with the same freshly prepared standard stock antigen solution.

RESULTS

The results of individual antibody determinations carried out on serum specimens of each rabbit on the ninth, twelfth, nineteenth and twenty-ninth days following antigenic stimulation are recorded in Table I. The amount of antibody is expressed in micrograms of antibody nitrogen per milliliter of serum. In those instances where supernate analysis after precipitation with 1 meg. antigen nitrogen revealed antigen in excess, the antibody content is expressed as zero; where treatment of a serum with 1 meg. of antigen nitrogen revealed a supernate in antibody excess, but where treatment of that serum with 2 meg. antigen nitrogen resulted in a supernate consistently in antigen excess, the antibody N is expressed as the mean R for that group.

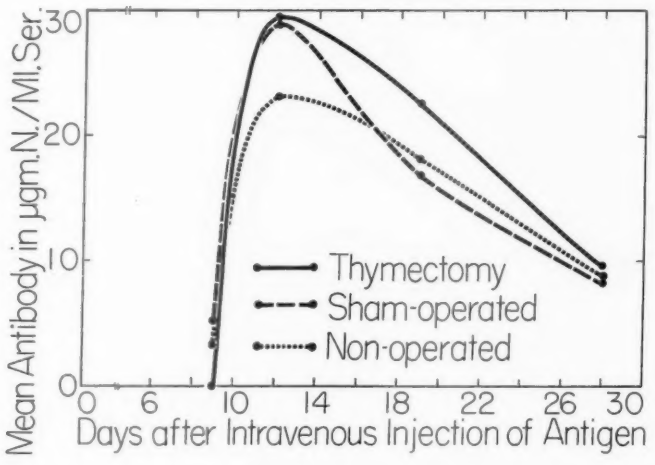


Fig. 3.—Graph plotting the levels of serum antibody against time following intravenous injection of bovine serum albumin in thymectomized, sham-operated, and nonoperated rabbits.

Table II summarizes a statistical analysis of the differences between means of the 3 groups, using a small sample technique, and the lack of significance between groups is further demonstrated in Fig. 3, wherein the mean antibody production for each group is plotted as a function of time after primary antigenic stimulation.

TABLE II. STATISTICAL COMPARISONS OF MEANS OF SERUM ANTIBODY PRODUCTION[8] IN THYMECTOMIZED, SHAM-OPERATED, AND NORMAL RABBITS

GROUPS COMPARED	12TH DAY	19TH DAY	29TH DAY
I and III	0.561	0.557	0.557
I and II	0.558	0.560	0.561
II and III	0.558	0.556	0.558

DISCUSSION

The simultaneous occurrence of two rare clinical conditions, acquired agammaglobulinemia and benign thymoma, reported herein, provoked an interest in assessing the role of the thymus in the immune response. It has been shown that the thymus gland of animals behaves differently in the immune response than the other lymphoid organs. Instead of developing plasmacytosis and producing antibody as do the lymph nodes, spleen, and bone marrow, the thymus of animals intensively immunized with several uni- and polyvalent antigens over prolonged periods does not develop plasmacytosis[1] or produce antibody.[1, 5] Using agglutination tests, Harris and associates[7] failed to show consistent differences in the immune response of thymectomized rabbits and litter mate controls. More recently, it has been shown[12] that extracts of thymus do not contain antibody, and tissue cultures of thymic tissue from previously immunized rabbits in contradistinction to other lymphoid tissue do not produce antibody. As a test of the possibility that the thymus might exert an inhibitory influence on antibody synthesis, the quantitative precipitin method was employed in this study in an effort to detect subtle differences in the responsiveness of thymectomized rabbits, as compared to controls with sham operations or not operated upon. That the thymus does not participate in the control of the immune response under the conditions described herein is indicated by the experimental findings. In spite of the data obtained in this investigation, which indicate that the normal thymus does not exercise a controlling influence on the immune response in the rabbit, it still seems likely that some essential relationship exists between the thymic tumor and the acquisition of acquired agammaglobulinemia. That the agammaglobulinemic condition was acquired in our patient is indicated by the history of a patient who was well without trouble from infection until he was 54 years old. Then suddenly, recurrent infections became his lot and over a period of four years he had at least 17 separate attacks of pneumonia, recurrent bacterial respiratory disease, and several attacks of septicemia. Soon after the onset of the clinical illness, a thymus tumor was discovered in association with abnormally low serum protein. Removal of the thymus tumor did not result in clinical remission of the respiratory disease and the existence of agammaglobulinemia was finally discovered. It is certain that, although acquisition of the agammaglobulinemia was temporally associated with development of thymoma, removal of the thymic tumor did not result in abatement of the immunological deficiency.

Whatever the relationship between the development of the thymus tumor and the acquisition of agammaglobulinemia may be, it seems unlikely that two such rare diseases have occurred together by mere fortuity. The recent discovery of another instance in which thymus tumor has been discovered in association with acquired agammaglobulinemia strengthens the conviction that the two phenomena are related in some essential manner. Determination of the nature of the relationship awaits further investigation.

SUMMARY

1. The simultaneous occurrence of benign thymoma and acquired agammaglobulinemia is reported.

2. That excision of the thymic tumor had no apparent effect on the enhanced susceptibility to infection in this patient is pointed out.

3. An essential relationship between the development of benign thymoma and acquisition of agammaglobulinemia in this patient is postulated.

4. Experiments demonstrating failure of total thymectomy to alter the production of antibody in the primary immune response are presented.

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A SIMPLE BUBBLE TYPE OF PUMP-OXYGENATOR FOR INTRACARDIAC SURGERY

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THE temporary by-pass of the heart and lungs by artificial maintenance of circulation and respiration has been accomplished by different pump-oxygenators with varying degrees of success.[2-7, 9, 10] The development of such a pump-oxygenator is usually beyond the limited means of an average surgical experimenter, mostly because of the tendency to overdevelop certain technical aspects.

Critical evaluation of different pump-oxygenators has prompted us to develop our own artificial heart and lung, where constant effort has been made to simplify all equipment without sacrificing its efficiency. This pump-oxygenator can be set up in any surgical laboratory allowing, after some experience, the exposure of the interior of the heart for twenty to twenty-five minutes.

EQUIPMENT

The apparatus consists of a double pump, oxygenator, plastic tubing for the extracorporeal circuit and polyethylene tubes for cannulas. There are no valves, debubblers, fibrin traps, level-sensers, or other automatic devices to increase error factors or nervous tension of the operating team. The oxygenator can be autoclaved, while the necessary plastic tubings are sterilized by 1/1,000 Zephiran solution.

Pump.—The only special equipment required for this mechanical heart and lung is the pumping unit, introduced by Dr. Lillehei and associates, currently used in controlled cross-circulation.

These double pumping units driven by a ⅓ horsepower electric motor equipped with individual speed changer and gear box are remarkably efficient and simple to operate, and cause only a negligible amount of hemolysis. The rate of flow is regulated by adjustment of the speed changer and the size of the tubing used. The flow in the circuits can easily be balanced by help of the speed controls after the average perfusion rate has been estimated.

Oxygenator.—The oxygenation is done by passing blood over blood oxygen foam as described by Waud,[15] and Gimbel and Engelberg.[8] In these bubble types of oxygenators, gaseous diffusion readily occurs when venous blood is perfused through an intricate pattern of a rising column of blood oxygen bubbles. The use of this counterflow principle fully oxygenates venous blood

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and at the same time adequately eliminates carbon dioxide. This system works with great speed and efficiency, comparable to the exchange which occurs through the respiratory alveoli in vivo. There is practically no hemolysis.

Preliminary laboratory examination showed that 1,000 c.c. of venous blood can be completely aerated in one minute by 6 liters of foam producing an increment of oxygen saturation from 70 to 98 per cent, while carbon dioxide content is decreased from 55 to 35 per cent. Spectroscopic absorption lines of this artificially oxygenated blood are between 575 and 585, corresponding with fully saturated arterial blood.

Blood cell destruction does not occur to any appreciable degree, since the value of free hemoglobin in blood recirculated through the oxygenator and reservoir was consistently below 0.4 per cent.

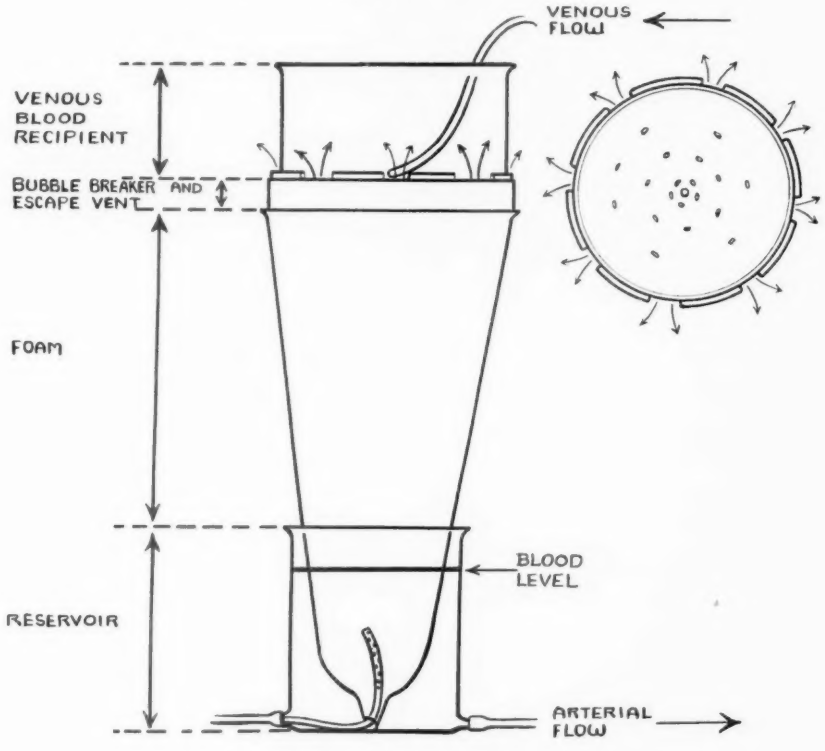

Fig. 1.—Oxygenator.

Air embolism does not constitute a serious risk, since the air bubbles are confined to the upper two-thirds of the oxygenator, distant from the outflow aperture which is located at the base of the apparatus.

The clotting of blood is prevented by 25 mg. heparin to every pint of blood.

A simple oxygenator was developed consisting of an 8,000 c.c. percolator and a 2,000 c.c. beaker. The percolator stands in the beaker and communicates with the latter through an aperture on the lower end. A recipient with numerous perforations at its bottom is joined loosely to the upper end of the

percolator by a 1-inch-high ring with small indentations. This ring is sprayed with Antifoam* and serves as a primitive bubble breaker and escape valve at the same time. When the beaker is filled with 1,500 c.c. of fresh arterial blood and 300 c.c. of plasma expander, some will pass into the lower one-third of the percolator to equalize levels. When oxygen is forced into the bottom of the percolator by a regular intranasal oxygen tube, a steadily rising aggregate of blood oxygen foam is produced within the upper two-thirds of the percolator. The bubbles, after oxygenating the descending venous blood, finally are either broken by the inrushing stream from the recipient, or disintegrated when touching the ring treated with Antifoam, thus eliminating carbon dioxide and superfluous oxygen from the system. The oxygenation of blood is plainly visible through the transparent wall of the percolator. The oxygenated blood collected in the bottom is used in part for the creation of new aggregates of foam, or alternatively passes into the beaker. The blood present in the lower one-third and neck of the percolator prevents bubbles escaping into the beaker. The beaker represents a primitive reservoir, from which the oxygenated blood can be pumped into an arterial system.

EXPERIMENTAL PROCEDURE

Large mongrel dogs were given 1,200 units of a long-acting Bicillin† and 50 mg. Pacatal,‡ a phenothiazine derivative, the night before surgery. Pacatal lowers the oxygen requirements of tissues and, by stabilizing the neurovegetative system, reduces the myocardial irritability and incidence of ventricular fibrillation.[1, 11] The next morning, after the animals are anesthetized with intravenous Nembutal, the Pacatal is repeated intravenously and 350 c.c. of 5 per cent glucose in distilled water with 1,000 mg. of tetracycline§ is started. The high coverage with antibiotics seems to protect dogs from shock and infection during the total by-pass. The chest is now opened through the right fourth intercostal space. Meticulous care is taken to obtain absolute hemostasis to prevent postoperative hemorrhage. Refraining from any further manipulation, No. 2-0 silk sutures are passed around both vena cava and azygos veins. The femoral vessels as well as the jugular vein and carotid artery are exposed and 5 mg. of Heparin per kilogram of body weight is given after all dissection is completed. Polyethylene catheters are now advanced into the superior and inferior vena cava, thoracic aorta, and carotid artery connecting the animal to the pump-oxygenator.

The pump and oxygenator are started with slow speed and the counterflow of venous blood and rising oxygen bubbles is balanced. The apparatus once properly functioning with a steady flow of 3 to 4 liters of oxygen will aerate any amount of venous blood from 100 c.c. to 1,000 c.c. without any further adjustment. The circuit checked and the blood level in the reservoir marked, the pumps are accelerated slowly until the heart decreases in size and the right atrium appears to be almost empty. This practically has indicated to

*Courtesy Dow Corning & Company.
†Courtesy Wyeth Laboratories, Inc.
‡Courtesy Promonta GMBH. Hamburg, W. Germany.
§Courtesy Roerig and Co.

us that most of the venous blood was channeled through the pump-oxygenator. Without any further delay the venae cavae and azygos vein are occluded and the right atrium or ventricle opened. The cardiac chambers are explored. If the coronary return excessively obscures the field the pumps are slowed down periodically. When septal defects are present, the left side is not sucked during repair, but kept filled all the time with physiologic saline solution by a small catheter. The tip of the catheter should be treated with Antifoam jelly to prevent bubble formation in the left side of the heart. We

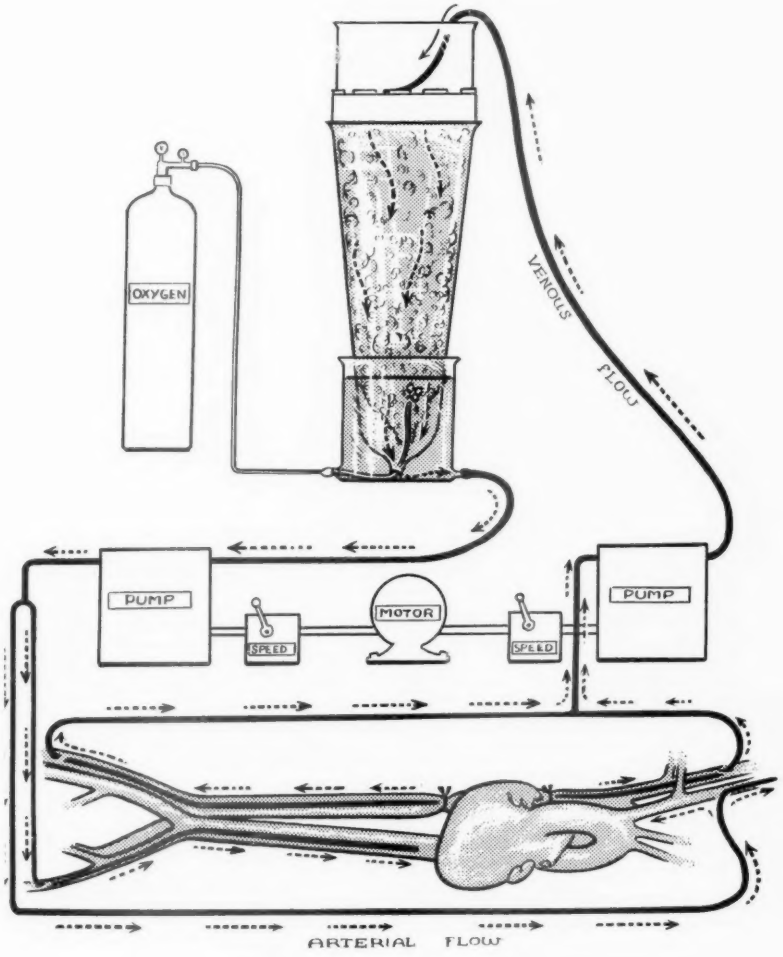

Fig. 2.—Pump-oxygenator.

do think that most septal defects can be closed in a few minutes, approximating the edges with interrupted sutures of No. 3-0 silk. In spite of the pump-oxygenator the time element is important and any tarrying inside the heart should be avoided. After the heart is allowed to be filled with coronary return the atrium is closed over a Satinsky clamp, or the ventricle by running suture. The superior vena cava and azygos vein are now allowed to empty again into the heart. The heart is usually responding well to the increased venous return with regular rhythm and vigorous beat. By simultaneous slow-

ing down of the pump-oxygenator the inferior vena cava is released. The loss of blood is estimated and replaced generously by a direct transfusion of fresh blood. In addition 2 ampules of protamine* are given in 250 c.c. of saline solution by a very slow intravenous drip. The chest is closed after a catheter is left in the pleural space for underwater suction drainage.

SUMMARY

A simple practical pump-oxygenator is described which has been successfully used to by-pass the heart and lungs of 25 dogs for periods of 15 to 25 minutes. In each experiment cardiotomy in a dry field was performed, permitting direct visualization of the interior of the right atrium or ventricle. The pump-oxygenator has been used with equal success during repair of auricular septal defects. Operative results and more detailed technical aspects will be reported in separate papers under preparation.

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*Courtesy Eli Lilly and Co.

DIRECT SUTURE ANASTOMOSIS OF THE CORONARY ARTERIES IN THE DOG

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THE importance of coronary artery disease has become progressively more apparent and the past twenty years has seen numerous attempts at surgical revascularization of the heart. These techniques have ranged from attempts at forming capillary anastomoses between the ischemic myocardium and various vascular extracardiac structures,[2] to reversal of arterial blood flow through the venous system of the heart as described by Beck,[3] or even to direct implantation of extracardiac vessels in the myocardium as described by Vineberg.[9]

Examination of the heart in severe coronary arteriosclerosis shows that the disease affects most severely the proximal portions of the major coronary branches.[4] Certainly, in many instances the atherosclerotic plaques are diffusely scattered throughout the coronary system and there are multiple points of stricture and occlusion. However, in a smaller percentage, the disease may be localized to a relatively short segment of the major arterial trunk. It is this latter group of cases which present a challenge to a surgical attack on the coronary vessels either by endarterectomy or by suture anastomosis.

The present work describes a technique for unhurried, precise anastomosis between a major coronary artery and an extracardiac vessel, in this case the internal mammary artery. It will be shown that blood flow can be maintained to the myocardium throughout the period of anastomosis. It is of some interest that some of these animals sacrificed as long as six months after the operation have shown widely patent anastomoses, though the vessels utilized for anastomosis had an internal diameter of less than 3 mm.

TECHNIQUE

In our experience acute occlusion of the main trunk of the left circumflex artery at its origin regularly resulted in the onset of ventricular fibrillation within three to five minutes. On the other hand, occlusion of the anterior descending branch was tolerated to a far better degree. Accordingly, it was felt that division of the left circumflex branch might be a more critical test of the efficiency of this technique in maintaining myocardial blood flow. As a source of extracardiac arterial blood the internal mammary artery was found to be anatomically the most suitable vessel. The dogs were anesthetized with

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Nembutal and respiration was maintained with an electrically-controlled respirator. A left thoracotomy was made through the bed of the fourth rib and, for additional exposure, the third rib was divided. This incision gave adequate exposure for mobilization of the left subclavian artery and its branches as well as for the approach to the coronary vessels.

The operation is commenced by incising the pleura over the subclavian artery and mobilizing this vessel and its branches. The various subclavian branches are then carefully dissected out and all the branches with the exception of the internal mammary are divided and ligated about 1 cm. distal to their origins (Fig. 1, *A*). The internal mammary artery is divided at a

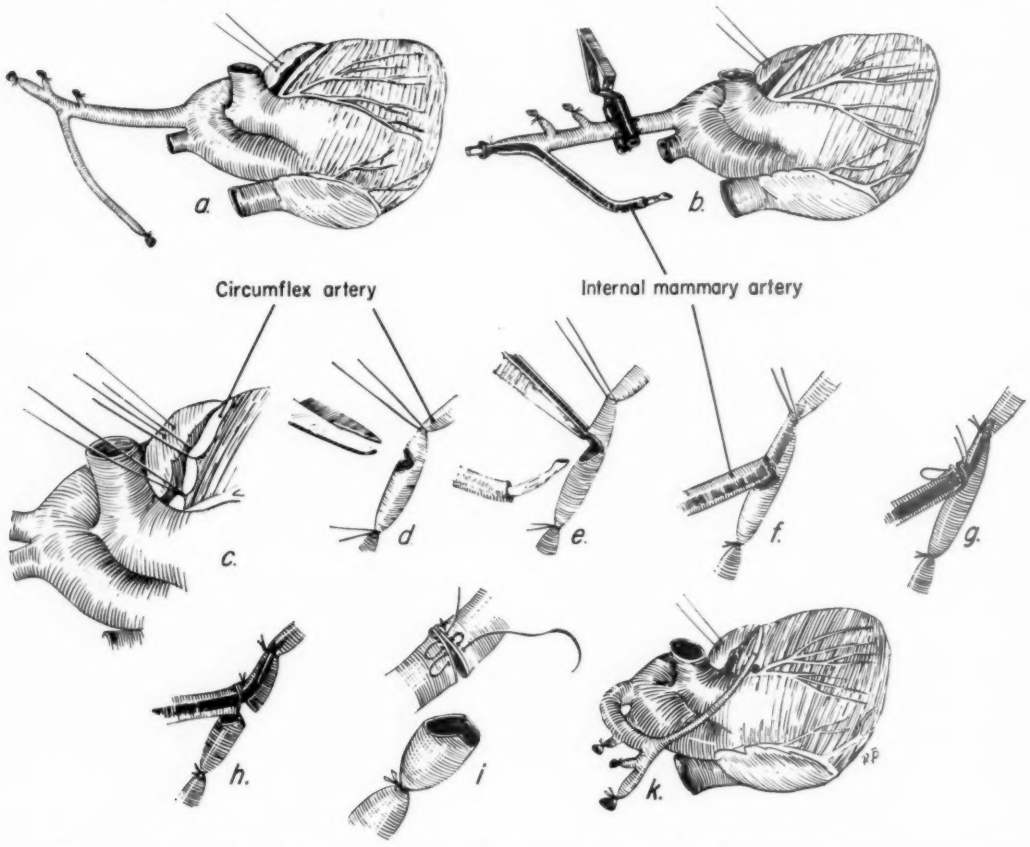

Fig. 1.—Composite sketch showing the technical detail of end-to-end internal mammary to coronary artery anastomosis. It will be seen (*B*) that the cannula carrying oxygenated blood is inserted into the arterial mammary artery by way of the vertebral branch of the subclavian artery. The completed anastomosis (*K*), should be compared with the arteriogram in Fig. 3.

convenient point, usually about 5 cm. from its origin. The whole subclavian trunk is then rotated in such a way as to approximate the internal mammary artery to the left circumflex artery under the least tension. The terminal centimeter of the internal mammary artery is then carefully prepared for anastomosis by removal of adventitious tissue.

While this part of the dissection is being performed, about 500 c.c. of arterial blood is collected from the femoral artery of a donor dog. This blood is collected in a standard vacuum bottle and coagulation is prevented by the

addition of small amounts of heparin. This bottle containing oxygenated heparinized blood is then arranged as shown in Fig. 2 so that blood can be delivered under controlled pressure. A glass cannula with blown olive tip was found to be most suitable for cannulization of the coronary artery, the curved limb being particularly useful for rotating the anastomosis.

The coronary vessels are now dissected free of the epicardial fat and the bifurcation of the left main coronary artery exposed. A 2-0 silk tie is placed loosely around the circumflex portion of the bifurcation and a rubber band ligature about 1 cm. distal to this point. The adventitious tissue is then cleaned off the coronary artery at the proposed site of anastomosis.

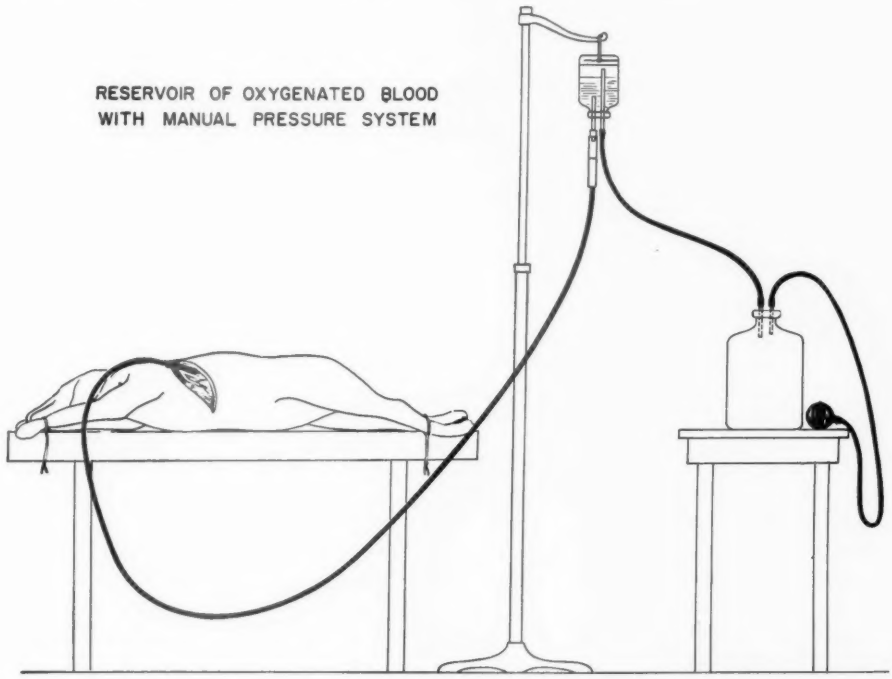

Fig. 2.—This diagram demonstrates the simple reservoir system used in delivering blood to the myocardium during the anastomosis. The large pressure bottle is used to maintain a constant head of pressure on the blood in the vacuum bottle. The rate of flow is calculated roughly during the procedure by passage of blood through the filter.

With the cannula now connected to the source of arterial blood, preparations for anastomosis can be made. First, the cannula is well coated with sterile mineral oil to reduce intimal damage and then it is inserted through the vertebral branch of the subclavian artery down the internal mammary artery. The vertebral branch is then securely tied around the base of the cannula. The internal mammary artery now slides freely over the tip of the cannula. The proximal tie around the circumflex artery is now secured and the anterior wall of the artery divided immediately distal to the point of ligation. The olive tip of the glass cannula is then inserted into the circumflex artery and secured in place by tightening the elastic tourniquet proximal to the olive tip (Fig. 1, *F* and *G*). The flow of arterialized blood is then started. It was our experience that a flow of 10 to 20 c.c. of blood per minute was quite sufficient to maintain a normal rhythm for periods as long as thirty minutes.

Once this flow of blood is established the anastomosis can be completed in an unhurried fashion. The anterior row of sutures is completed before dividing the posterior wall of the circumflex artery. This helps to steady the vessel during the insertion of the first sutures. A running everting mattress stitch of 6-0 silk was used. After completing the anterior row, the posterior wall of the circumflex artery is divided, the needle passed under the artery and the anastomosis rotated so that the posterior wall comes to lie anteriorly. This greatly facilitates the precise placement of the sutures along the posterior wall. Great care is taken throughout the anastomosis to obtain a precise intima to intima approximation using a large number of finely placed stitches situated as

Fig. 3.—Arteriogram obtained by injection of Diodrast into the base of the aorta via a cannula in the carotid artery. The caudad angulation of the subclavian artery may be seen. The arrow demonstrates the internal mammary artery and its anastomosis with the left circumflex coronary artery.

close to the margin of the vessels as possible. At the completion of the anastomosis the rubber tourniquet is released from around the glass cannula and the ligature holding the cannula in the stump of the vertebral artery divided. The cannula is then quickly withdrawn, the stump of the vertebral artery secured with a clamp and the bulldog clamp occluding the subclavian artery quickly removed, once again allowing aortic blood to flow into the internal mammary artery and thence into the left circumflex coronary artery. The anastomosis

is now complete and any slight leak generally responds to gentle pressure with a sponge. In general, the anastomoses were completed in five to ten minutes but in order to test the efficiency of the system some were purposely prolonged for as long as thirty minutes without signs of myocardial arrhythmia. It should be added that a number of end-to-side anastomoses were attempted and, though they were technically more difficult and time-consuming, survivors were

Fig. 4.—Autopsy specimen of a dog sacrificed six and one-half months after anastomosis showing widely patent anastomosis. This is the same animal as was used for the arteriogram illustrated in Fig. 3.

obtained. Moreover, autografts using femoral vein and femoral artery were anastomosed between the aorta and the left circumflex coronary artery. The venous grafts proved to be unsuitable but several survivors with the arterial grafts were obtained.

RESULTS

In the initial skirmishes with this problem, a large number of animals were operated upon to determine the most suitable technique for maintaining blood

flow to the myocardium during the period of anastomosis. The immediate survival of these animals appeared to depend mainly on two factors. First, it was necessary to cannulate the ligated circumflex artery expeditiously in order to perfuse the ischemic myocardium with oxygenated blood. Second, on withdrawing the cannula it was necessary to have an anastomosis of such proportion as to support flow through the circumflex artery. Approximately 50 per cent of the animals survived the immediate procedure. During the learning period a number of animals developed ventricular fibrillation when, due to inexpert cannulation, the ventricular myocardium remained ischemic for longer than two minutes. During the first two weeks after operation, further animals were lost. The cause of death in the group centered chiefly around a technically poor anastomosis. Thus, some animals died of hemorrhage or empyema and the remainder of thrombosed or strictured anastomoses. With increasing experience it was possible to do the operation with greater facility and precision, thereby increasing the survival rate to about 75 per cent.

Long-Term Survival With Patent Anastomosis.—The major problem in small blood vessel anastomosis has been early thrombosis and progressive stricturing of the anastomosis. Indeed, it is often said that anastomoses of vessels of less than 0.5 cm. in diameter will inevitably become occluded. To study this problem further in the coronary vessels, 17 animals were operated upon in the standard fashion and allowed to survive from two to six and one-half months. At the time of sacrifice these animals were all in vigorous health. To test the patency of the anastomoses, angiocardiography was performed, injecting Diodrast into the base of the aorta by means of a plastic cannula inserted by way of the carotid artery. The patency of these anastomoses was confirmed by direct palpation of the vessel distal to the point of anastomosis by angiocardiography and by dissection of the anastomotic area. Furthermore, the healing of these anastomoses was studied by microscopic section. Of the 17 animals in this group, patent anastomoses were found in 7.

These patent anastomoses, as shown in Fig. 4, show no evidence of stricturing; the intimal lining was smooth and regular and multiple sections through the myocardium revealed no gross or microscopic evidence of cardiac damage. Examination of these anastomoses prior to sacrifice revealed excellent pulsation in the internal mammary and in the circumflex coronary branch distal to the site of anastomosis.

DISCUSSION

The present study indicates the feasibility of small blood vessel anastomosis within the range of an internal diameter of 2 to 3 mm. While coronary artery suture anastomosis was demonstrated as early as 1940 by Gordon Murray,[6, 7] no demonstration of long-term survival with widely patent anastomoses has hitherto been accomplished. The most important factors determining the success of these anastomoses appear to be the meticulous and precise approximation of intimal surfaces and the avoidance of trauma to the circumflex artery by the distal ligature. To allow the unhurried and careful performance of these anastomoses then, the necessity of providing oxygenated blood to the ischemic myocardium throughout the anastomosis is of prime importance. The

volume requirements of blood are small enough in the dog to pose no important problem and oxygenated blood may be secured by any one of several methods of which the simplest are probably those described by Warden[10] and by Callaghan and Gerbode.[5] Alternatively, where large-volume blood flows are desired (and this should rarely be necessary), an oxygenator of the bubble type may be used.

Whether or not techniques such as the present one may be directly applied to human coronary artery disease is open to speculation. The two great complicating factors in the human disease are, first, the presence of multiple atherosclerotic strictures situated throughout the ramification of both branches of the coronary artery and, second, the probability that these anastomoses would have to be made to vessels whose walls were to a greater or lesser degree diseased. While it is true that the majority of patients dying with severe coronary artery disease have fairly diffuse involvement of the major branches by atherosclerotic deposits, yet cases are not infrequently found where the disease is dominantly situated in the proximal few centimeters of the major branches. In a study of 30 hearts from patients with severe arteriosclerotic heart disease, the site of occlusion was such that anastomosis would have been technically feasible in five.[8] In these cases direct anastomosis might be applicable. Perhaps even more suitable would be those cases where the ostia alone are involved, such as in syphilitic aortitis.

SUMMARY

A technique is described for direct anastomosis of an extracardiac vessel, in this case the internal mammary artery, to the circumflex coronary artery. During the anastomosis oxygenated blood was shunted through the site of anastomosis. It was shown that long-term survival with widely patent functional anastomoses could be secured by using this technique. Possible clinical applications are discussed.

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SURGICAL EXPOSURE OF THE AORTIC VALVE

An Experimental Study

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In 1914 Carrel,[1] working with Tuffier, reported a method for open operation on the pulmonary and aortic valves. He concluded, "It is not impossible that some day surgeons will be able to cauterize valvular lesions or to repair them as we do today in our experimental operations." With the aid of hypothermia open operations are now being used in the treatment of pulmonary stenosis and interatrial septal defects. It appeared that direct vision surgery of the aortic valve would offer advantages over the indirect methods presently employed. The following technique has been used in order to permit exposure of the aortic valve for periods of 3½ to 4 minutes.

METHOD

Fifteen adult mongrel dogs weighing 9 to 17 Kg. were anesthetized with intravenous thiopental sodium. Following endotracheal intubation, intermittent positive pressure oxygen and ether were administered. The dogs were immersed in an ice and water bath until their rectal temperature fell to 35° C. They were then removed from the bath and placed on the operating table. The temperature usually drifted to 31°-33° C. by the time circulatory occlusion was instituted. In 10 consecutive animals the right chest was opened through the fourth intercostal space. (In an additional animal the ascending aorta was exposed through an incision in the left fourth intercostal space.) Temporary ligatures were placed around the superior and inferior venae cavae and the pericardium was opened anterior to the phrenic nerve. A ligature was tied around the tip of the right atrial appendage for retraction. The ascending aorta was freed of the overlying fat pad and a heavy silk ligature passed around it. A stay suture of 3-0 arterial silk was placed in the adventitia on the lateral side of the aorta at the sinus of Valsalva of the noncoronary cusp (Fig. 1). A curved Potts clamp was applied to the lateral wall of the aorta as close as possible to the base of the heart. Exposure of the base of the aorta was facilitated by retraction of the superior vena cava laterally and the right atrium inferiorly. A vertical incision 2.5 cm. in length was made in the excluded portion of the aortic wall and Allis clamps were applied to its

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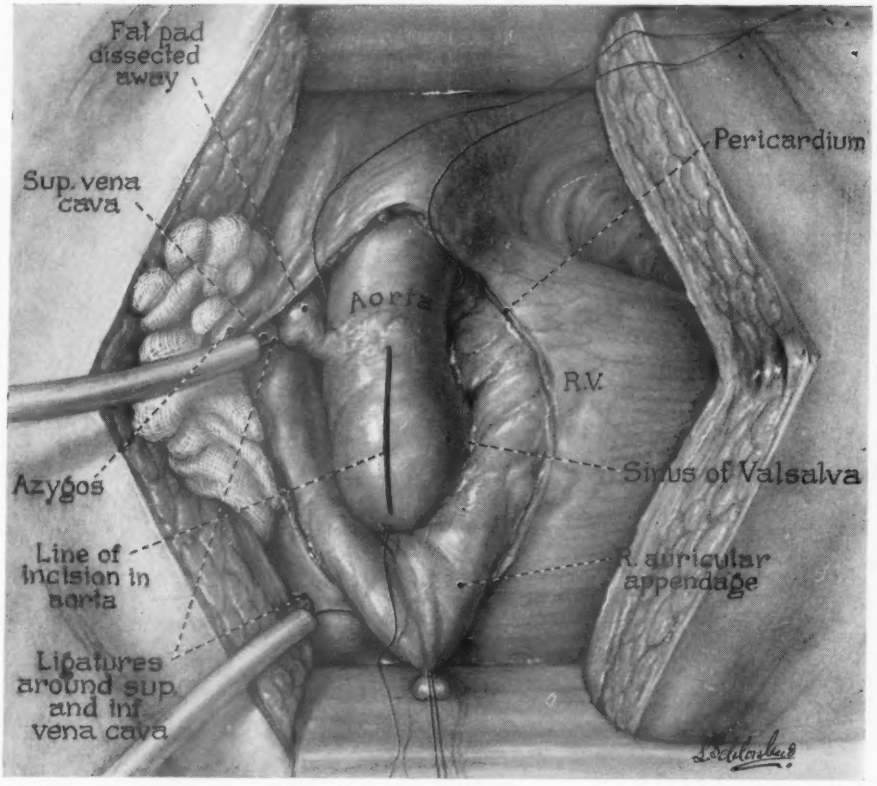

Fig. 1.—Exposure of the right lateral ascending aorta; the line of incision is indicated.

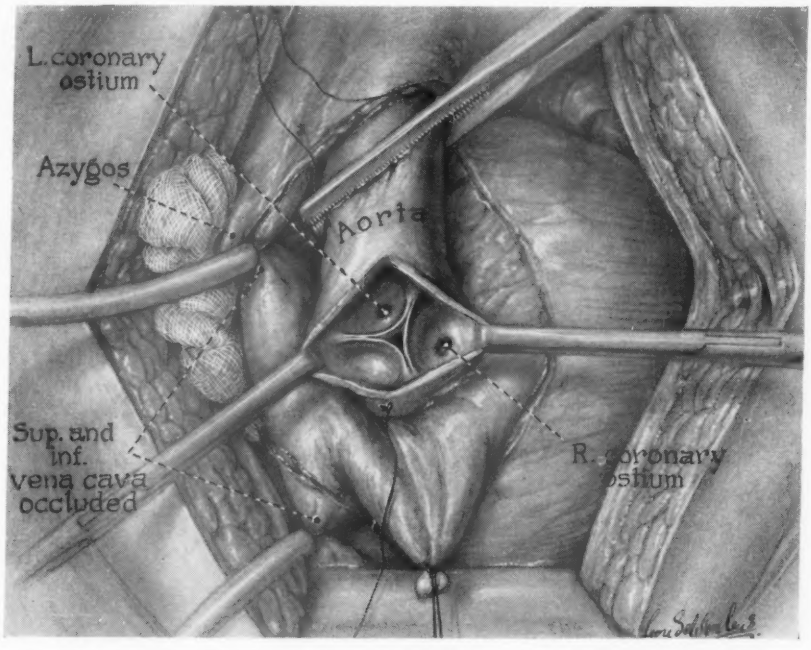

Fig. 2.—Operative exposure of the aortic cusps and coronary ostia.

edges. At this time the ether was discontinued and the animals maintained on 100 per cent oxygen for the remainder of the procedure. In six animals atriocaval infiltration[2, 3] was performed immediately before inflow occlusion with 5 c.c. of 1 per cent Xylocaine.

The superior and inferior venae cavae were occluded and the aorta was cross-clamped immediately proximal to the brachiocephalic artery. The Potts clamp was removed from the aortic incision, and residual blood aspirated from the ascending aorta and left ventricle (Fig. 2). The aorta was open for 3½ minutes. At the end of this period, both cavae were released and within 30 seconds the resumption of flow from the left ventricle flushed all air from the proximal aortic segment. The Potts clamp was reapplied and the clamp

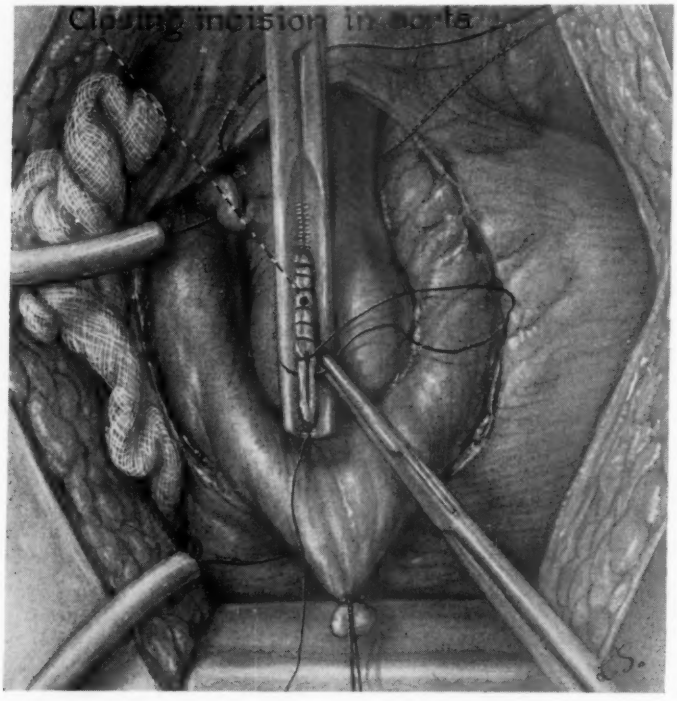

Fig. 3.—Closure of the aortic incision following restoration of circulation and removal of air.

occluding the aorta was removed. The inflow to the heart was regulated by means of the ligatures around the cavae, and the coronary perfusion was improved when indicated by partial occlusion of the aorta by means of the encircling ligature. In 3 dogs careful regulation of the inflow and outflow was necessary to restore a vigorous beat. The aortic incision was closed with an over-and-over continuous suture of 3-0 arterial silk (Fig. 3). The pericardium was left open and the chest was closed in layers. The animals were allowed to warm spontaneously.

In four additional animals air was purposely trapped in the aorta and left ventricle before restoration of the circulation at 3½ minutes. This was accomplished by clamping the aortic incision before release of the caval ligatures. Atriocaval infiltration was used in one of these animals.

RESULTS

In 11 consecutive dogs the aortic valve was exposed for 3½ to 4 minutes without the occurrence of ventricular fibrillation or air embolism. Ten of these procedures were carried out through the right chest and one through the left. The left thoracotomy provided poor exposure of the aortic cusps and coronary ostia compared to the right. In four additional animals in which air was purposely trapped in the left ventricle and in the ascending aorta at the time of restoration of the circulation, large quantities of air were visible in both main coronary arteries and their branches. Within 10 to 15 seconds the hearts became flabby and cyanotic, and beat poorly. This was in contrast to the previous 11 hearts in which air was not trapped. The inflow of blood was carefully regulated to prevent overdistention of the right atrium while the ascending aorta was partially occluded in order to increase the coronary perfusion. This technique was successful in washing the air out of the coronary arteries within one minute in all 4 animals. The hearts became pink and developed good tone. Ventricular fibrillation or standstill did not occur. There was no evidence of brain damage in any of the 15 animals. All animals were ambulatory the night of operation or the next day and were returned to the general colony by the fourth postoperative day.

DISCUSSION

Before beginning these experiments it was considered that coronary air embolism would be an obstacle to direct vision exposure of the aortic valve. However, in this series there was no evidence of air embolism to the heart, brain, or peripheral circulation. During the period that the ascending aorta was open, blood could be seen in the coronary ostia. This blood was not propelled by cardiac contraction and its level remained flush with the inside of the aortic wall. While the aorta was open, neither blood nor air entered the coronary ostia. At the end of the period of exposure, air embolism was prevented by releasing the cavae and carefully flushing the air from the left ventricle and aorta. In the 4 animals in which the aortic incision was closed without evacuating the air, coronary air embolism always occurred. This was successfully treated by the regulation of venous inflow and partial occlusion of the ascending aorta. Cardiac massage was never necessary.

The myocardial anoxia resulting from the interruption of coronary perfusion is the important factor limiting the time during which the aorta can be safely opened. Of almost equal importance is the careful regulation of venous inflow during restoration of the circulation. If too much blood is allowed to return to the heart at this time, failure may ensue. Judicious use of partial occlusion of the aorta is a useful adjunct. By this means coronary flow can be increased immediately after restoration of the circulation with rapid return of good color and tone to the myocardium. The heart is then able to tolerate complete caval release within a few minutes.

In order to obtain good exposure of the aortic cusps the aortic incision must be made as close as possible to the base of the heart. In the dog, this is

made possible by placing the incision in the free area on the right lateral wall of the aorta. This region is easily exposed, without dissection, by retraction of the superior vena cava and the right atrium. If the incision is too high, exposure is limited by the diameter of the aorta. An anterior incision must necessarily be placed higher than a lateral one because of the overlying right ventricle.

SUMMARY

The aortic valve was exposed for 3½ to 4 minutes in 11 consecutive dogs. This was accomplished with hypothermia and inflow occlusion. There was no instance of air embolism or ventricular fibrillation. The technique should be applicable in reparative surgery of the aortic valve under direct vision.

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TECHNIQUE FOR END-TO-END ANASTOMOSES BETWEEN ARTIFICIAL GRAFTS AND ARTERIES WITH MINIMAL INTERRUPTION OF THE CIRCULATION

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THE placement of an artificial graft in the resection of a great vessel like the aorta is a risky operation, principally due to the necessity of interrupting the blood stream for a prolonged period of time. Even experienced and skillful surgeons need about twenty-five minutes to place a synthetic prosthesis in place; this is generally due to personal factors such as the high nervous tension to which the surgeons are subjected during that time, and such inherent difficulties in these operations as the hazardous work of the end-to-end anastomoses between the synthetic fiber and the artery wall. Very often the time goes over limits quite dangerous for the patient. It is a well-known fact that the longer the blood stream is interrupted, the greater the risk; and this risk is in direct relation to the proximity of the heart, especially if the interruption deprives the central nervous system of blood flow. Even with the improvements which have been made to relieve this situation, the time element is still a great problem.

In order to overcome this difficulty, different techniques have been established. In spite of their ingenuity and their effectiveness in some cases, they usually are hazardous and inappropriate for routine use.

Generally, these techniques are based on shunts or by-pass,[15, 16] either by using human vessels or artificial tubes made of plastics such as polythene. Years ago, Alexis Carrel,[4] suggested the use of a tube temporarily placed between the ends of the vessel while doing an end-to-end anastomosis. This tube has to be removed before the last anastomosis has been completely accomplished. Recently, Charles A. Hufnagel[11, 12] improved this method by successfully employing a polythene tube. In our opinion, this method has real value because it reduces the time of interruption considerably.

Recently, James D. Fryfogle,[9] from the Henry Ford Hospital in Detroit, proposed a method of rapid anastomosis based on the principles that we shall describe later, with a brief interruption of the circulation by using a removable prosthesis placed exteriorly to a homograft over which a rapid end-to-end suture is made.

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This technique gives excellent results when used with homografts as they recommended but, in our experience, it is not properly used with grafts made of synthetic fibers, as they have to be placed in a special manner.

In working with artificial grafts and considering that these synthetic fibers give excellent results,[13] we developed the method proposed in this paper.

This technique has been proved in experimental animals and on one patient. Five dogs with a body weight varying between 25 and 35 pounds were used for this purpose. At this weight the aorta is of adequate size to enable us to work with a certain facility. These animals were previously checked and prepared for the experiment. In all instances a Dacron graft, about 2 inches long, was placed in the thoracic aorta. The first animal was sacrificed ten minutes after the operation; the second, at one hour; the third, at forty-eight hours; and the fourth, at fifteen days. The fifth animal, at this time, fifteen weeks after the operation, is in perfect health.

Examinations of these grafts were made which proved that all of them were functioning perfectly well. No vascular damage could be found, as can be seen in the photograph of the one from the dog that was sacrificed fourteen days after the operation (Fig. 1).

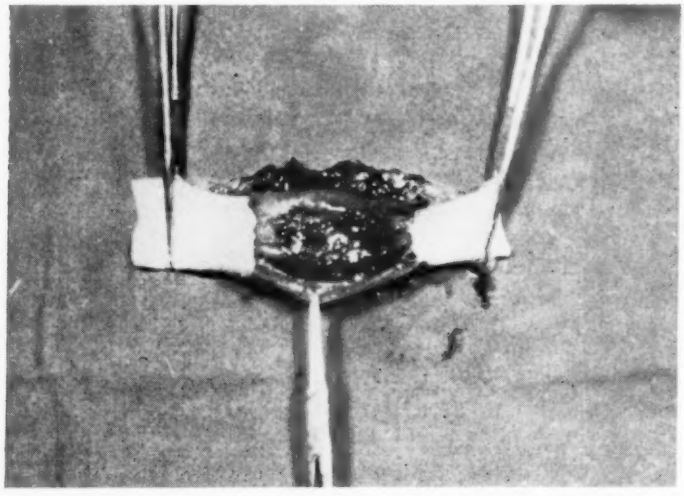


Fig. 1.—Dacron graft removed fifteen days after operation.

Then the technique was employed in a human being, a 53-year-old man, with a Leriche syndrome of about six years' duration. Blood supply to the lower limbs was about zero, with continuous and severe pain. The procedure gave excellent results, and the circulation was interrupted for only six minutes.

To facilitate the explanation of this method, we divide it into two parts: (a) the removable prosthesis, and (b) modus operandi.

1. *Removable Prosthesis.*—This is a small tube similar to the one used by Blakemore and Lord[1-3] with certain modifications. It is made of Plexiglas or any other similar plastic material, because in our opinion the tubes made of such material give the best results. In spite of the essential purpose of this prosthesis, which is to connect both ends of the severed vessel, this one has a fundamental difference in it.

While the Blakemore tube is used permanently, the one we propose is used only to permit a rapid re-establishment and maintenance of the blood stream during the time the end-to-end suture is made between the artificial graft and the artery.

Description of the prosthesis: It is made of Plexiglas or any other similar plastic material.

A longitudinal slot about 0.5 mm. wide has been made from one end to the other, in such a way that the tube is opened longitudinally (Fig. 2). Diametrically against this cut a similar slot has been made but, in this instance, the wall is partially excised. The purpose of the cuts is to permit the tube to be broken when its use is over.

About 2 mm. from one end there is a circular groove wherein the artery is tied together with the graft (Fig. 2). Immediately above this groove, and parallel with it, there is a concavity which is made to facilitate the passage of the needle.

We want to point out that the exterior surface is not completely smooth in order to prevent the sliding of the synthetic fiber and the artery wall.

2. *Modus Operandi.*—The procedure we propose is based on an old and well-known method which is the use of tubes made of different materials and placed externally to the blood vessels in order to make the end-to-end anastomosis of the vessels. This is done by introducing the vessel through the tube and folding the end around it; then the whole is shuffled into the artery and tied around. This is inconvenient, especially in large vessels, as this circular ligature, after a few days, and because of the localized ischemia, frequently produces a necrotic zone which could be followed by a rupture of the artery wall with the consequent hemorrhage. Therefore, this may cause thrombosis at this level.

It was Nitze[14] in 1897, who, for the first time, employed ivory rings to do the permanent anastomoses of the blood vessels. These rings were not well tolerated by the surrounding tissues. Rings of different materials were used afterward[13] with poor results.

Then in 1942, Blakemore, Lord and Stefko[1] made their well-known tube of Vitallium, a metal which had been discovered at that time and which was known to be inert in the organism. This prosthesis has been widely used, not only for vessel anastomoses but for other purposes, in its original shape or slightly modified. With time, this system has been almost discarded because it is a well-known fact that the results obtained are frequently mediocre.

Size of the artificial graft to be used: Considering that when the tube is removed, the artificial graft increases somewhat in length, the retraction of the severed artery is in some way compensated and the best result is obtained by choosing a graft of about the same length as the defect. We want to point out that we are referring to the length of the graft already placed in the removable prosthesis and with the ends bent.

The width of the graft should be one that adjusts perfectly around the removable prosthesis, and this should be of such a size that it can be introduced easily into the artery, as follows: With the aid of a compass, we measure

the external diameter of the artery in millimeters. From this measurement, we subtract 3 mm. and this new measurement is probably, with none or just a little error, the correct diameter which should be employed. To facilitate things, the best method is to prepare different prostheses in advance with their grafts, ready to be used.

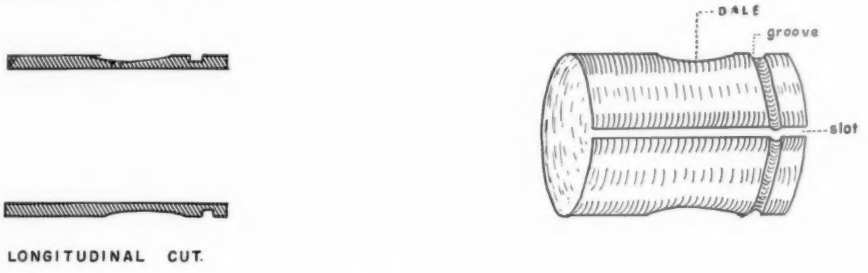


FIG. 2

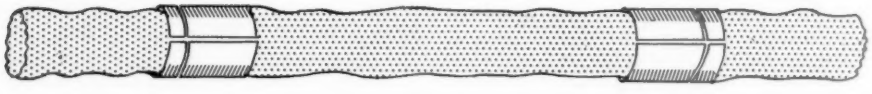


FIG. 3

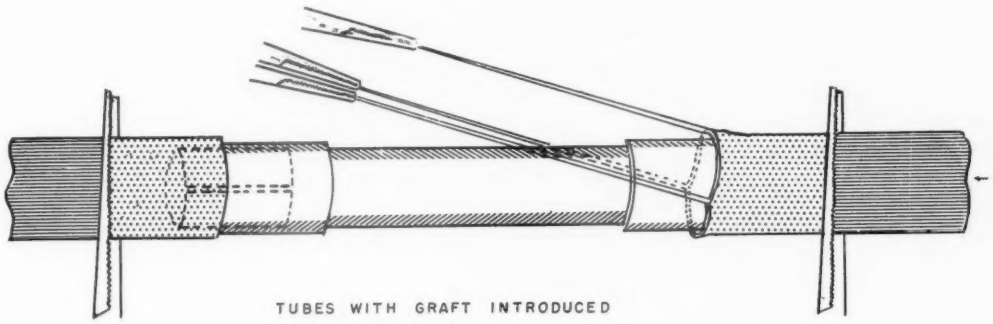
SYNTHETIC GRAFT INTRODUCED THROUGH THE TUBES

FIG. 4

GRAFT'S ENDS EVERTED

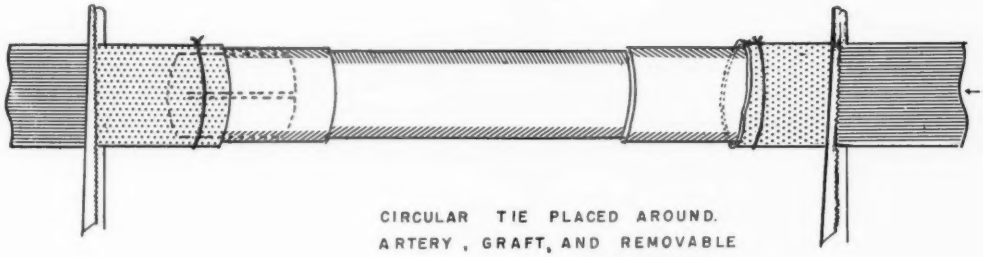
Procedure: 1. After having selected the graft and the tubes which are going to be used (Fig. 3), we introduce the end of the graft into the corresponding prosthesis, and then evert it around the referred tube (Fig. 4). The everted portion of the graft should overlay about 0.5 cm. of the rear end of the tube, enough to let us cover the suture line when finished, as is usually done.

2. To interrupt the blood flow, the aortic clamps should be placed with special care as far as possible from the place where the artery is going to be excised. This is to prevent the ends becoming too short because of the re-



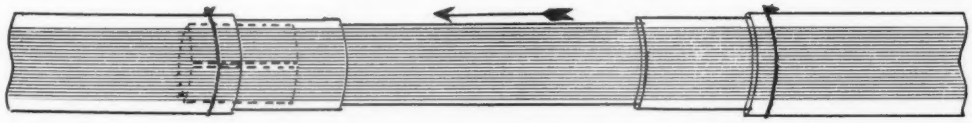
TUBES WITH GRAFT INTRODUCED INTO ARTERY ENDS

FIG. 5



CIRCULAR TIE PLACED AROUND ARTERY, GRAFT, AND REMOVABLE PROSTHESIS

FIG. 6



CIRCULATION REESTABLISHED

FIG. 7

traction of the artery wall, in which case the tube cannot be placed properly and the clamps ought to be placed farther away from the line of excision.

3. The introduction of one end of the graft with its corresponding tube into one of the ends of the artery (Fig. 5) should be done in such a way that

the free border of the artery should overlay by about 5 mm. the circular groove of the tube, in which place it is tied by means of 0 silk thread (Fig. 6).

This thread has to be fastened just enough to obtain a good hemostasis and to prevent the sliding of the artery but, at the same time, it cannot be so tight as to produce damage to the artery wall.

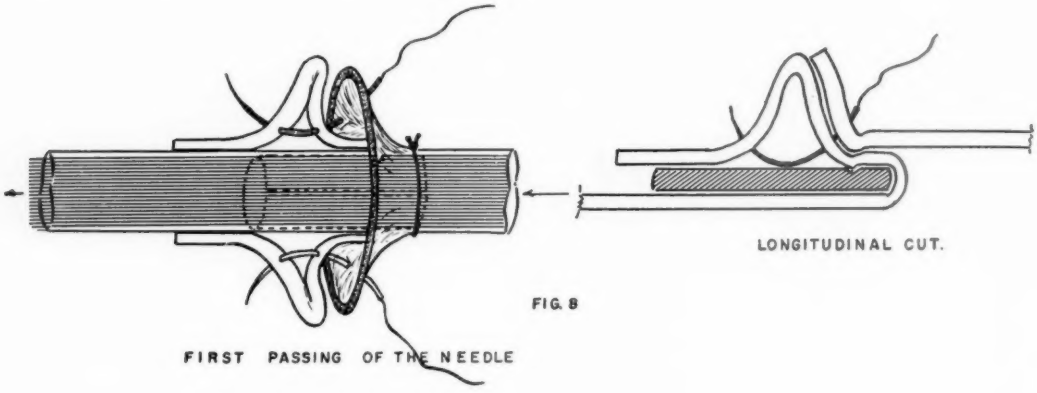


FIG. 8

FIRST PASSING OF THE NEEDLE

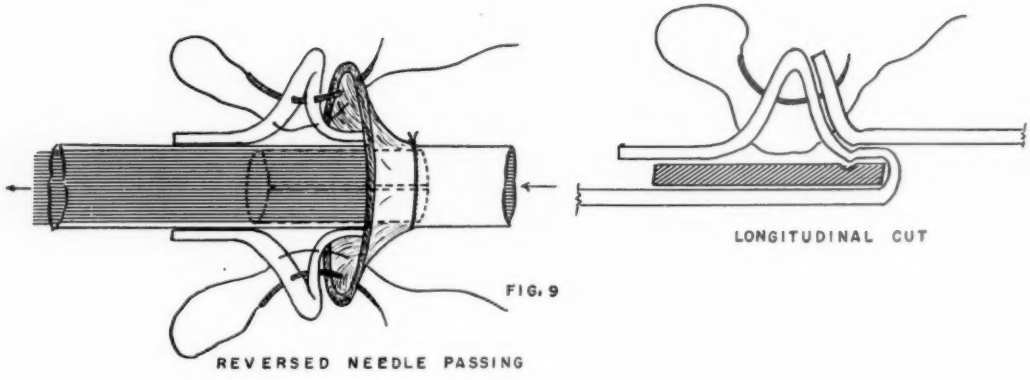
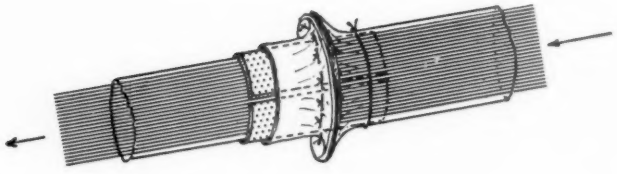


FIG. 9

REVERSED NEEDLE PASSING



END-TO-END SUTURE COMPLETED

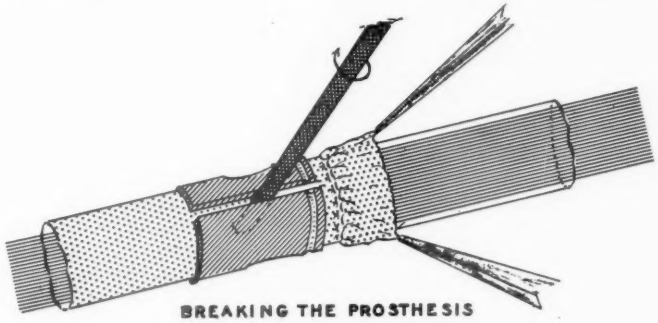
FIG. 10

In several experiments that we have performed, it has been proved that an adequate pressure for this purpose does not produce any damage to the artery, as was mentioned previously.

4. Re-establishment of the circulation by removing the occlusion clamps (Fig. 7) has to be done carefully in order to check possible bleeding at the site of the circular tie, and to prevent shock.[10]

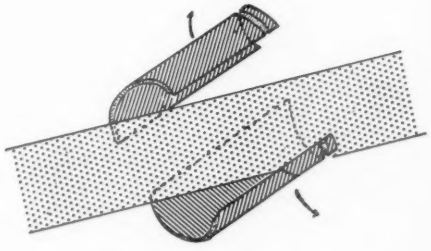
5. With the blood running through the graft, we proceed to the end-to-end Carrel type suture[4-8] between the synthetic fiber and the artery wall. This can be done easily and with less worry to the surgeon since he knows that he does not have to rush. To do this, we proceed as follows:

a. The needle is introduced through the free end of the artery wall a few millimeters from the circular tie, parallel to the longitudinal axis of the artery, and is withdrawn through the fiber. In this way the needle has gone twice through the graft wall and only once through the artery wall (Fig 8).



BREAKING THE PROSTHESIS
WITH SHARP INSTRUMENT

FIG. 11



BROKEN REMOVABLE-PROSTHESIS REMOVED

FIG. 12

b. Reversing the needle, we proceed in the same way, but this time the needle is introduced first through the fiber, 2 or 3 mm. from the point of emergence of the thread (Fig. 9), and withdrawn through the artery.

c. The thread is tied and we have completed a U stitch which places together in an evert manner the artery wall and the double end of the synthetic graft.

We place as many stitches as necessary to complete the whole suture between the graft and the artery (Fig. 10). After this is accomplished, the

artery is clamped again, and the circular ties around the tubes are removed. Then we open the clamps gently to check bleeding at the suture line and, in case it is necessary, we place additional stitches to produce a perfect hemostasis.

Generally it is not necessary to place additional stitches because the use of our tubes helps us to do the suture in an easier, more even, and accurate manner. The suture line is then covered with the free portion of the synthetic fiber, reversing it above as it is commonly done.

Removal of the prosthesis: A sharp instrument (knife holder) is carefully introduced into the slot of the tube (Fig. 11) which is then broken by dividing it in two parts. The two parts or pieces are then taken out (Fig. 12).

SUMMARY

A new technique has been proposed to perform the everted end-to-end anastomosis between artificial grafts and arteries with minimal interruption of the circulation, using a removable prosthesis, and an original technique has been described for making the suture over a removable tube.

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THE REPLACEMENT OF LONG AND NARROW ARTERIAL SEGMENTS

An Experimental Study of Heterografts and Seamless Woven Nylon and Teflon Prostheses

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DESPITE the recent advances in the methods of procurement and storage of human arterial homografts and notwithstanding the excellent early clinical results obtained with them, the intense interest in arterial substitutes of other than human origin continues both because of the promise of ease of availability and simplicity of handling that lyophilized heterografts and plastic prostheses offer and because of the apprehension professed by many concerning the ultimate fate of homogenous arterial implants. In the past, the experimental methods employed in the search for better graft material involved, with very few exceptions,[14] the use of short and narrow vascular segments, as a rule segments of the aorta. Yet, owing to the frequency of femoropopliteal arterial occlusive disease and to the difficulty of obtaining homogenous arteries suitable for use in their grafting therapy, the clinical demand for vascular substitutes approximating the dimensions of the human femoropopliteal arterial trunk is urgent. The great scarcity of information concerning their behavior as implants has, therefore, prompted us to undertake an experimental investigation of long and narrow segments of heterogenous artery and seamless woven plastic—in particular, teflon—tubes as arterial substitutes.

MATERIAL AND METHOD

Segments of bovine carotid arterial heterografts and of seamless woven tubes of teflon, purified teflon, and nylon were transplanted to healthy male mongrel dogs weighing 10 to 20 Kg. The experimental groups were as follows: heterografts, 20 dogs; teflon, 10 dogs; bleached teflon, 10 dogs; and nylon, 10 dogs. A group of 20 dogs with arterial homografts of similar dimensions served as control.

Both the aortic homografts from sacrificed laboratory animals and the heterografts collected at the slaughterhouse were taken without aseptic precautions. The grafts were processed according to the method used in our artery bank.[13, 23, 24] After their removal the vascular segments were trimmed, sterilized with betapropiolactone, lyophilized, and stored under vacuum. The heterografts were common carotid arteries from the calf and the range of their size matched quite closely the variations in the size of dog aortas (Fig. 1, *a*). The plastic seamless woven tubes had been prepared in three diameters, 7.5, 8.5, and 10 mm., and were cut to proper length just before insertion; heated scissors were used to seal the ends and prevent fraying. The segments of appropriate dimensions were sterilized by

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autoclaving. The length of the grafts and prostheses ranged from 18 to 24 cm. The nylon* prosthesis had been woven of yarn of 200 denier and the thread count of the fabric was 60 x 40 (Fig. 1, *b*). The plastic teflon* is a relatively new compound that has not found much biological application in the past (Table I).[3, 12, 17] It is a tetrafluoroethylene resin and its physicochemical properties are characterized by nonadhesiveness and extreme inertness and stability. In course of the manufacturing process teflon fiber acquires a dull dark-brown color presumably due to the formation of carbonaceous impurities. By treating successively with alkalis and concentrated inorganic acids, teflon fabric can be bleached to a snowwhite color.† The prostheses here designated as "bleached teflon" were so treated; before use appropriate measures were taken to return the pH of the fabric to neutral. The weight of the teflon yarn was 400 denier and its thread count 60 x 40.

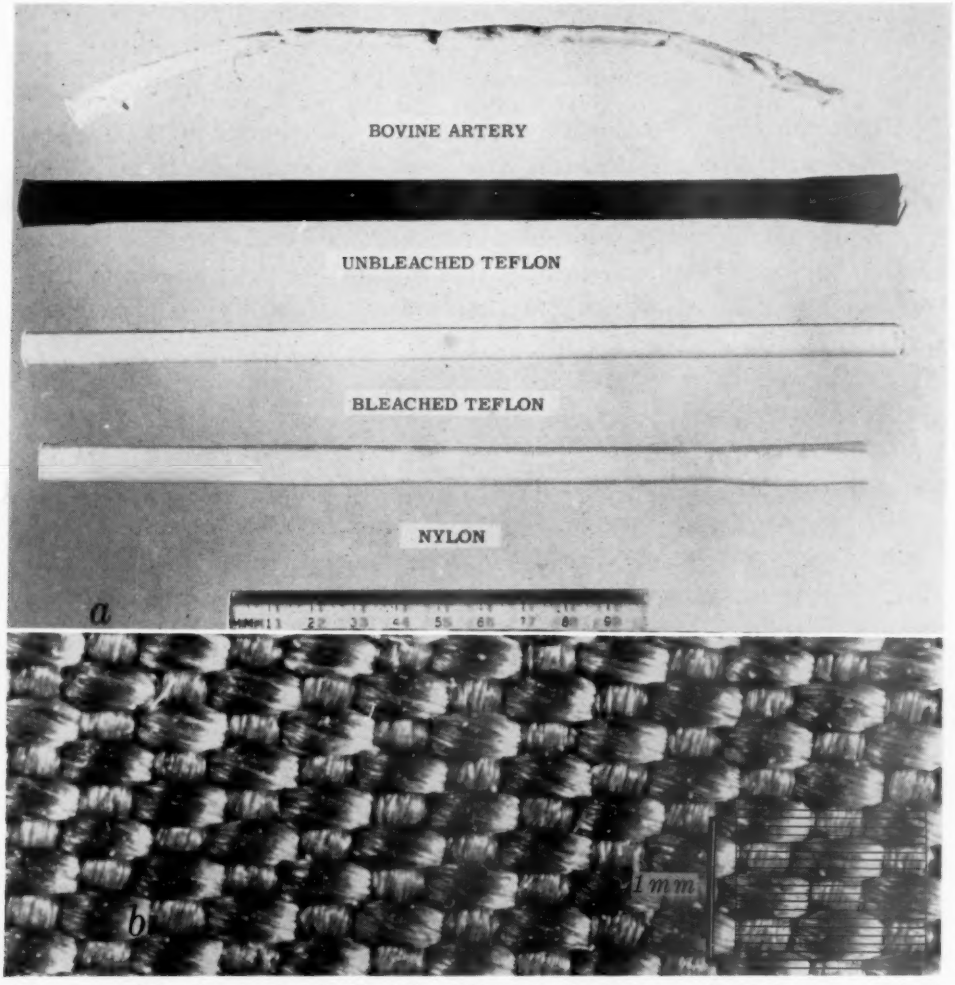

Fig. 1.—*a*, The chemically sterilized lyophilized bovine heterograft (before reconstitution) and the seamless woven plastic prostheses used in the experiments; the ranges of dimensions were 7.5 to 10 mm. (diameter) and 18 to 24 cm. (length). *b*, The weave of the plastic prostheses (taffeta), with a thread count of 60 × 40.

The grafting procedure employed was essentially the same as described by McCune and Blades[14] under the designation of Method B (Fig. 2, *a*). Two incisions were utilized; through a left flank incision access was gained to the abdominal aorta, and through a left

*The nylon and teflon fiber used had been manufactured by the E. I. Du Pont de Nemours Co., Inc., Wilmington, Delaware. Until the time of the present writing teflon had been available only in 400 denier yarn with 60 filaments.

†The bleaching process consists in boiling the fabric 24 hours in concentrated sulfuric acid at 540° F., 24 hours in concentrated nitric acid at 212° F., 24 hours in 50 per cent sodium hydroxide at 212° F., and 24 hours in aqua regia at 212° F.

thoracotomy in the seventh or eighth intercostal space the thoracic cavity was entered and the desired level of the aorta at D_8 or D_9 was reached. First the distal anastomosis was performed, which was an anastomosis between the obliquely cut end of the graft or prosthesis and the side of the abdominal aorta at a point just distal to the inferior mesenteric artery. The graft or prosthesis was then carried into the left chest in a retroperitoneal and retropleural tunnel through a hiatus made in the posterior attachment of the left leaf of the diaphragm. At the chosen level (D_8 or D_9) the thoracic aorta was now cut across between clamps and an end-to-end anastomosis was made between the proximal end of the graft or prosthesis and the proximal stump of the thoracic aorta. The distal stump of the cut aorta

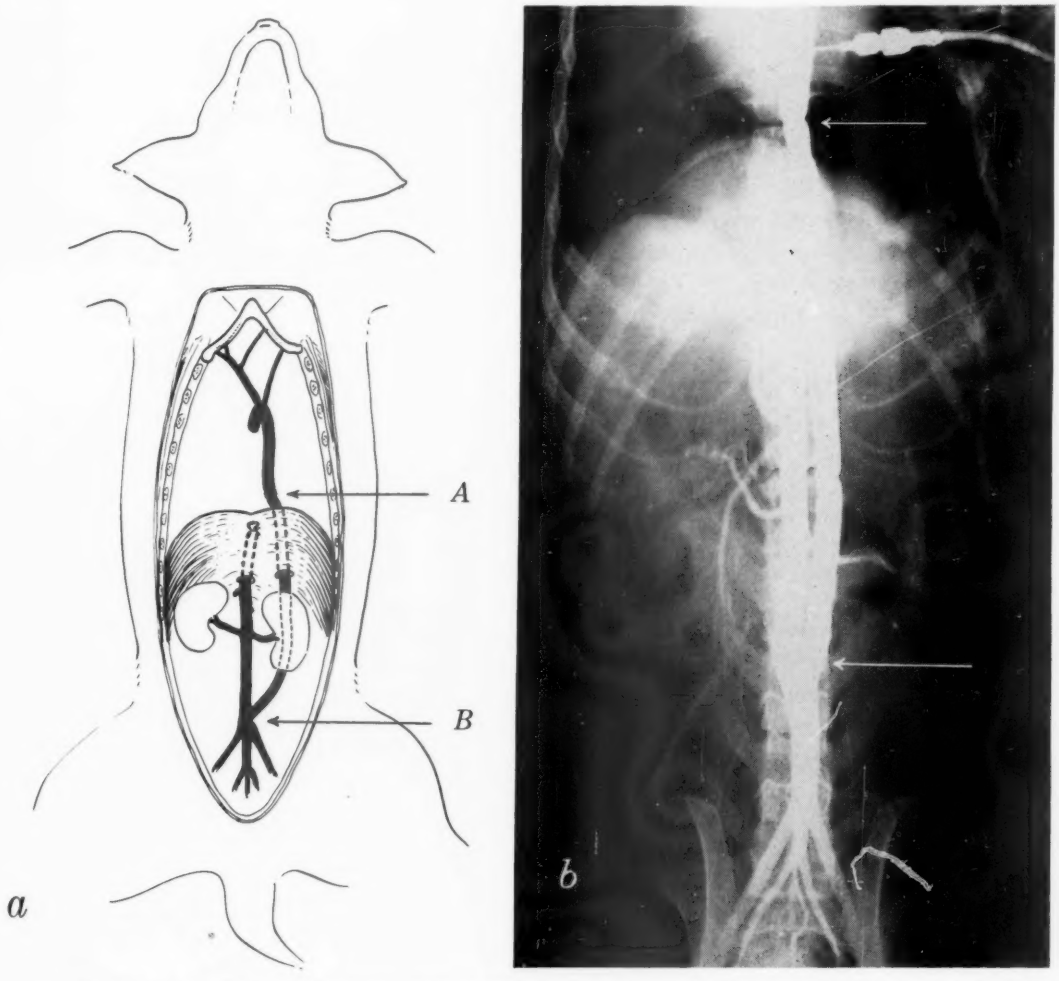

Fig. 2.—*a*, The experimental preparation; *A* and *B* denote the proximal and distal extremities, respectively, of the graft or prosthetic implant. *b*, Aortogram taken directly before sacrifice.

was sewed over in two layers. Using 5-0 arterial silk on an Atraumatic needle, the distal anastomosis was made with an over-and-over continuous stitch, whereas the proximal anastomosis was secured with an everting horizontal continuous mattress suture. Anesthesia was obtained with ether-oxygen mixture, and during the open thoracotomy a mechanical respirator was utilized. Anticoagulants were not used and antibiotics were given only in those instances where gross operative contamination was recognized or when evidence of sepsis occurred in the postoperative period. This procedure is a time-consuming and traumatic one and the operative mortality rate among the dogs was high, especially during the first part

of the period of experimentation while the technique was being mastered. Only those animals which survived more than forty-eight hours were considered in evaluating the results of the study.

Observations were made regarding the general condition of the hosts and the quality of the pulse distal to the graft or prosthesis. The animals were sacrificed at stated intervals, which generally were 2 weeks, 1 month, 2 months, 4 months, 6 months, and 8 months postoperatively. In each experimental group at least one animal was allowed to survive for one or more years. Agonal aortograms (Fig. 2, *b*) were often obtained at the time of sacrifice. After the removal of the graft or prosthesis the specimens were studied for gross characteristics as well as microscopic structure.

RESULTS

The behavior of the grafts and protheses was evaluated on the basis of their functional state during life and of the gross and microscopic changes observed at sacrifice. As regards the functional state in vivo, the experiment was so designed that failure of the graft to remain completely patent led to almost instantaneous death. Some degree of narrowing of the lumen of the implant was, however, compatible with life, and the presence of such a complication was reflected in the nutritional state of the animal or in the angiographic findings obtained just before sacrifice (Table I).

TABLE I. PROPERTIES OF TEFLON (TETRAFLUOROETHYLENE RESIN) AT 77° F.

Tensile strength	1,800 pounds per square inch
Shearing strength	3,800 pounds per square inch
Flexural strength	Unbreakable
Water absorption	0.0 per cent
Resistance to weathering	Excellent
Chemical reactivity	Attacked only by molten alkali and fluorine

Sources of data: Cornell,[6] and Reference Sheet.[17]

Homografts.—In the 20 animals comprised in this group (Table II, Fig. 3, *a* and *b*), 18 were studied after sacrifice or death at intervals ranging from one week to 9 months; 2 dogs were kept alive and these are well at 13 and 14 months. Among the 18 dogs examined 2 died as a direct result of the failure of the graft. The grafts in these animals showed localized deposits of fibrin undergoing organization and resulting in a marked narrowing of the arterial lumen. The remaining 16 dogs can be considered graft successes although 2 of these died of causes not related to the graft; at autopsy, however, the grafts of the last-named animals were entirely satisfactory. One animal classified among the successful results which was sacrificed at 2 weeks had a graft with minimal intimal fibrin deposits. In the remaining 15 dogs the graft showed a smooth intimal surface with only very small fibrin deposits at scattered points and a well-preserved parietal structure supported in a connective tissue framework of adequate but not excessive amount. The connective tissue reaction in 8 of these instances appeared to be somewhat more marked than one would optimally expect.

The histologic findings in the homografts both as to structural detail and as to the evolution of the tissue changes were in complete agreement with the findings formerly reported by numerous investigators.[1, 5, 7, 8, 15, 16, 19, 22]

TABLE II. RESULTS OF HOMOGRAFTS

DOG NO.	FOLLOW-UP	FATE OF HOST	AORTOGRAM	GRAFT GROSS CHARACTERISTICS: REACTION AROUND GRAFT	GRAFT GROSS CHARACTERISTICS: LUMINAL SURFACE	RESULT	REMARKS
CG-36	1 week	Sacrificed	Patent	++	I	Good	
CG-12	10 days	Expired	0	+++	I	Good	Empyema
CG-33	2 weeks	Sacrificed	Patent	+	I– (StF)	Fair	
CG-34	2 weeks	Expired	0	+	I– (StF)	Poor	
CG-35	3 weeks	Sacrificed	Patent	+	I	Good	
CG-27	3 weeks	Expired	0	+++	I	Good	Malnutrition
CG-24	1 month	Sacrificed	Patent	++	I	Good	
CG-30	1 month	Sacrificed	Patent	+++	I– (P)	Good	
CG-29	2 months	Sacrificed	Patent	+++	I	Good	
CG-28	3 months	Sacrificed	0	+	I– (U)	Good	
CG-21	5 months	Sacrificed	Patent	+	I– (U, P)	Good	
CG-23	5 months	Sacrificed	0	+	I– (U, P)	Good	
CG-25	6 months	Sacrificed	0	++	I– (P)	Good	
CG-26	7 months	Sacrificed	Patent	+	I– (P)	Good	
CG-20	7 months	Sacrificed	0	+	I– (P)	Good	
CG-18	7 months	Sacrificed	Patent	+	I	Good	
CG-10	9 months	Expired	0	++	I– (StF)	Poor	Fibrous stenosis
CG-13	9 months	Sacrificed	Patent	++	I– (P)	Good	
CG-10	13 months	Under observation	0			Living and well	
CG-14	14 months	Under observation	0			Living and well	

+ = mild, ++ = moderate, +++ = marked; I = intact luminal surface; I– = smooth, glistening intimal surface with one or more of the following imperfections: Th = small organized mural thrombus, StF = stenosing fibrous deposit, U = superficial ulceration.

TABLE III. RESULTS OF HETEROGRAFTS

DOG NO.	FOLLOW-UP	FATE OF HOST	AORTOGRAM	GROSS CHARACTERISTICS: REACTION AROUND GRAFT	GROSS CHARACTERISTICS: LUMINAL SURFACE	RESULT	REMARKS
HG-55	7 days	Sacrificed	Patent	+	I	Good	
HG-25	8 days	Expired	—	N.D.	N.D.	Poor	Rupture
HG-23	9 days	Expired	—	+	I– (DU)	Poor	Rupture
HG-19	10 days	Expired	—	+	I– (DU)	Poor	Rupture
HG-51	12 days	Expired	—	+	I– (DU)	Poor	Rupture
HG-54	2 weeks	Sacrificed	Patent	+	I– (P)	Good	
HG-52	3 weeks	Sacrificed	Patent	++	I– (P)	Good	
HG-27	1 month	Expired	—	+++	DU	Poor	Rupture
HG-58	1 month	Sacrificed	Patent	+	I– (SU,D)	Fair	
HG-25	6 weeks	Sacrificed	—	+	I-(SU)	Good	
HG-32	2 months	Sacrificed	Patent	+	I– (P)	Good	
HG-39	3 months	Sacrificed	—	+++	I– (P)	Good	
HG-29	3½ months	Expired	—	+	I– (DU,A)	Poor	Rupture
HG-47	4 months	Sacrificed	Patent	+	I– (P)	Fair	
HG-40	6 months	Sacrificed	Patent	+	I– (P)	Good	
HG-33	7 months	Sacrificed	Patent	+	R– (P)	Fair	
HG-30	9 months	Sacrificed	Patent	+	A	Poor	
HG-28	13 months	Under observation				Living and well	
HG-24	13 months	Under observation				Living and well	
HG-20	13 months	Under observation				Living and well	

DU = deep ulceration; A= aneurysmal dilatation; R = irregular intimal surface due to extensive ulceration and for fibrin deposit. See also key of abbreviations for Table II.

Heterografts.—Of the 20 animals in this group (Table III, Fig. 4, *a-d*), 11 were sacrificed at intervals ranging from 1 week to 9 months, 6 died in 8 weeks to 3½ months because of hemorrhage from the graft, and 3 are living and well at 13 months. Among the 11 dogs that were sacrificed on schedule, 10 grafts were considered satisfactory, but 3 in this group showed moderately

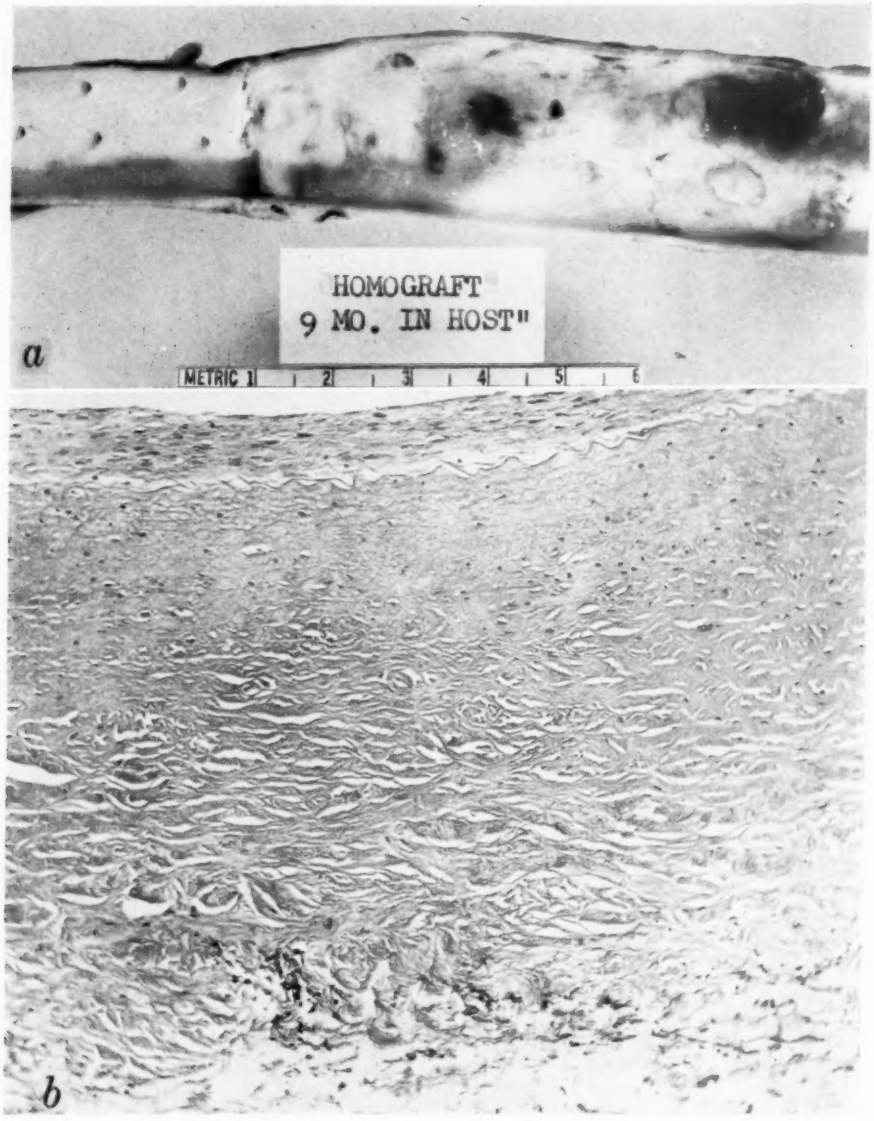

Fig. 3.—*a*, View of the proximal portion of a homograft 9 months after implantation; host aorta to the left. Dark areas are small agonal deposits of fresh fibrin. *b*, Photomicrograph (×70, reduced ½) of the same specimen. The usual degenerative changes are seen, with early fibroblastic ingrowth and mild periadventitial reaction.

severe degenerative changes. One graft removed at 9 months after implantation was made up entirely of a series of confluent aneurysmal dilatations. Five of the 6 grafts that ruptured showed areas of deep ulceration and one revealed an aneurysmal dilatation near the distal end. Minor imperfections were noted

in 7 of the 10 successful grafts, the most frequently observed one being the presence of tiny organized mural thrombi, as described in the homografts. Histologic sections in the successful heterografts showed changes similar to those in the homografts with a somewhat greater degree of connective tissue reaction in the host. The changes in the grafts that ruptured were extensive

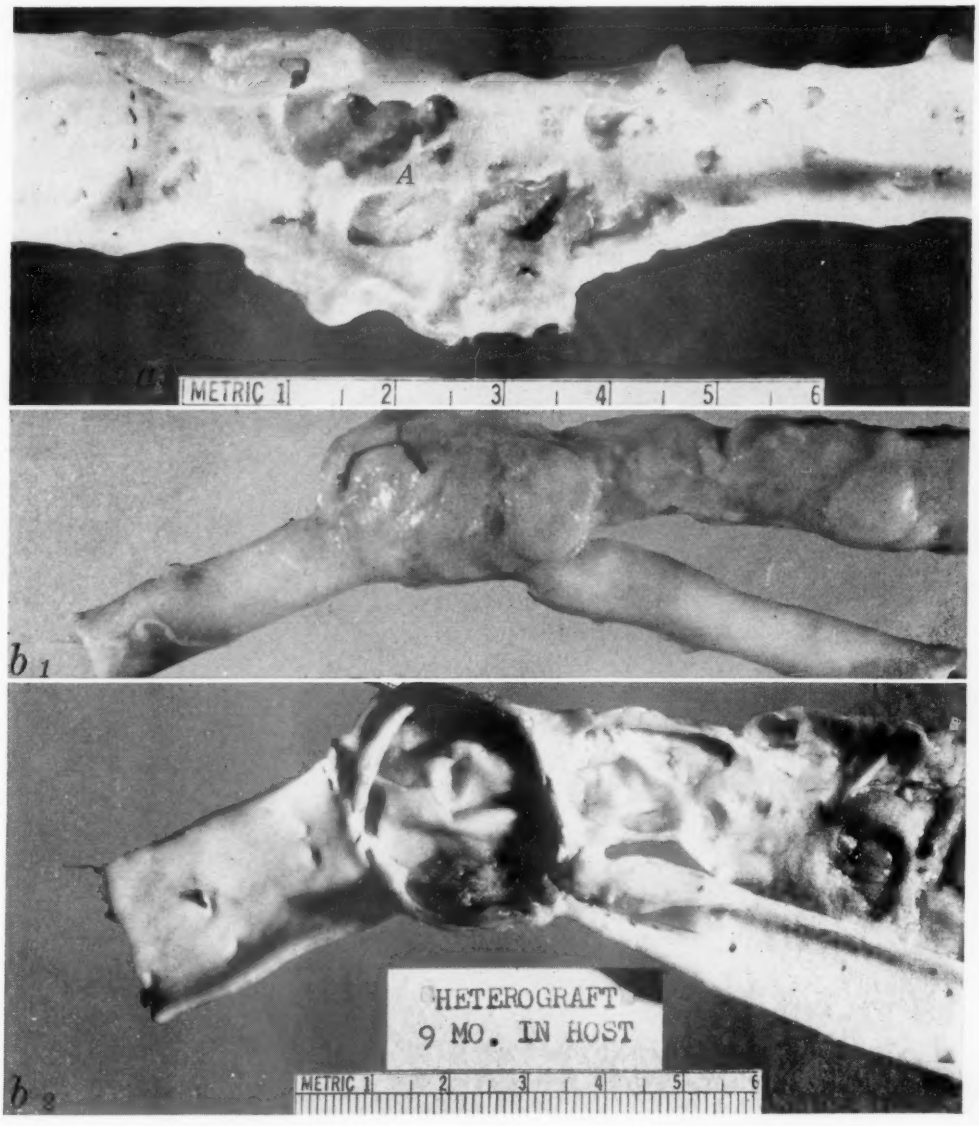

Fig. 4.—*a*, Bovine heterograft 4 months after implantation. Extensive ulceration of the intima with necrosis of the media; *A* denotes site of rupture. b_1, Caudal portion of heterograft 9 months after implantation. Extensive aneurysmal dilatation of the graft. b_2, Same as b_1, opened.

necrotic degeneration of the elastic laminae, ulceration of the intima, and marked leukocytic infiltration in the adventitia with either a complete lack of connective tissue reaction or an excessive amount of scarring in the periadventitial layer (Fig. 4, *c*).

Nylon.—Among the 10 dogs in this group (Table IV, Fig. 5, *a* and *b*) 4 are living and well at 6 weeks to 6 months after implantation. Three animals were sacrificed at 8 days to 3 weeks, and 3 animals expired in a state of severe malnutrition. In the 3 cases referred to last, the prostheses showed marked stenosis due to partially organized mural thrombi at the site of moderate

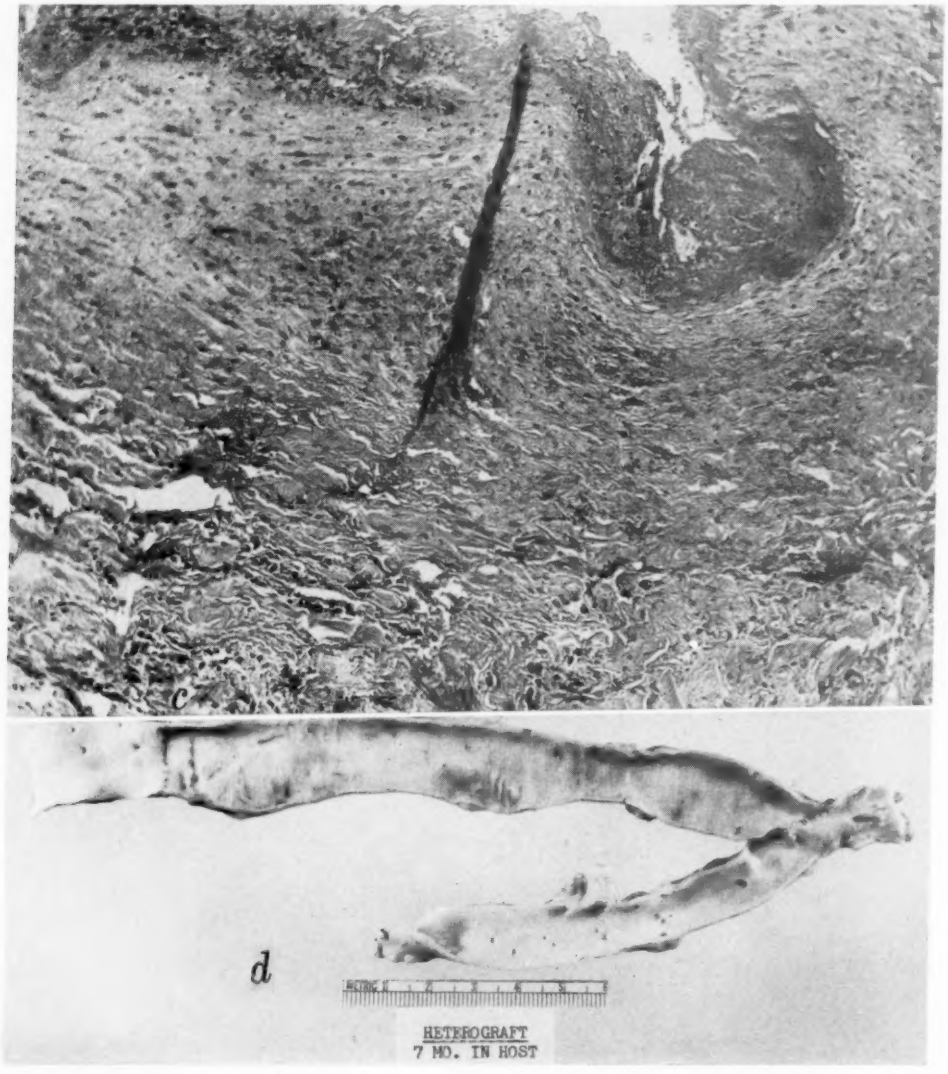

Fig. 4 (Cont'd).—c, Photomicrograph (×70, reduced ½) of wall of heterograft 4 months after implantation. Ulceration of the intima with fibrinous and leukocytic exudate. Advanced necrobiotic changes of the media. The periadventitial reaction is mostly leukocytic. *d*, Overall view of a heterograft that functioned well until sacrifice at 7 months; considerable intimal destruction is seen. (Host aorta to the left and at bottom.)

wrinkling. The remaining portions of these prostheses showed no measurable imperfections. In the sacrificed animals, histologic examination of the implants (Fig. 5, *c*) disclosed an orderly structural arrangement of the wall of the new-formed vascular tube similar to that observed in the teflon prostheses (*vide infra*), but with a greater amount of connective tissue proliferation than seen in the latter.

TABLE IV. RESULTS WITH NYLON

DOG NO.	FOLLOW-UP	FATE OF HOST	AORTO-GRAM	GRAFT GROSS CHARACTERISTICS: REACTION AROUND GRAFT	GRAFT GROSS CHARACTERISTICS: LUMINAL SURFACE	RESULT	REMARKS
NG-20	8 days	Expired	–	+	I	Good	
NG-12	9 days	Expired	–	+	I– (NF)	Good	
NG-17	3 weeks	Sacrificed	–	+	I– (P,SW)	Good	
NG- 9	1 month	Expired	–	+	I– (SF,MW)	Poor	Malnutrition
NG-24	6 weeks	Sacrificed	–	+	I (SF,MW)	Good	
NG- 8	3 months	Expired	–	+	I– (SF,MW)	Poor	Malnutrition
NG-10	5 months	Expired M	–	+	I– (SF,MW)	Poor	Malnutrition
NG-13	6 months	Sacrificed	–	+	I– (SF,MW)	Good	
NG-21	5½ months	Under observation				Living and well	
NG-15	6½ months	Under observation				Living and well	

NF = areas of nonepithelialized fibrous tissue; SW = slight wrinkling; MW = moderate wrinkling. See also keys of abbreviations for Tables II and III.

TABLE V. RESULTS WITH TEFLON (UNBLEACHED)

DOG NO.	FOLLOW-UP	FATE OF HOST	AORTO-GRAM	GRAFT GROSS CHARACTERISTICS: REACTION AROUND GRAFT	GRAFT GROSS CHARACTERISTICS: LUMINAL SURFACE	RESULT	REMARKS
TG- 7	1 week	Sacrificed	–	+	I	Good	
TG- 9	2 weeks	Expired	–	++	I	Good	Empyema
TG- 6	5 weeks	Expired	–	++	I– (SF,MW)	Poor	Malnutrition
TG-14	7 weeks	Sacrificed	Patent	+	I–P	Good	
TG-16	3 months	Sacrificed	Patent	+	I–(P,SW)	Good	
TG- 5	4 months	Sacrificed	Patent	+	I– (NE,SW)	Good	
TG-15	4½ months	Expired	–	+	I– (SF,MW)	Poor	Malnutrition
TG-10	6 months	Sacrificed	Patent	+	I– (NE,SW)	Good	
TG-11	8 months	Under observation				Living and well	
TG-13	8 months	Under observation				Living and well	

See Tables II, III, and IV.

TABLE VI. RESULTS WITH TEFLON (BLEACHED)

DOG NO.	FOLLOW-UP	FATE OF HOST	AORTO-GRAM	GRAFT GROSS CHARACTERISTICS: REACTION AROUND GRAFT	GRAFT GROSS CHARACTERISTICS: LUMINAL SURFACE	RESULTS	REMARKS
TPG-26	3 weeks	Sacrificed	--	+	I	Good	
TPG-37	3 weeks	Expired	--	++	I	Good	
TPG-19	7 weeks	Sacrificed	--	+	I– (SW)	Good	
TPG-32	4 months	Sacrificed	Patent	+	I– (SW)	Good	
TPG-34	4 months	Sacrificed	Patent	+	I– (P)	Good	
TPG-29	5 months	Sacrificed	Patent	+	I– (P,MW)	Good	
TPG-17	6 months	Sacrificed	Patent	+	I	Good	
TPG-23	6 months	Under observation				Living and well	
TPG-24	6 months	Under observation				Living and well	
TPG-25	6 months	Under observation				Living and well	

See Tables II, III, and IV.

Teflon.—Among the 10 dogs (Table V, Fig. 6, *a-c*) 5 were sacrificed on schedule within from 1 week to 6 months, 2 expired of malnutrition, and 1 died of empyema. The animals that expired of malnutrition had prostheses

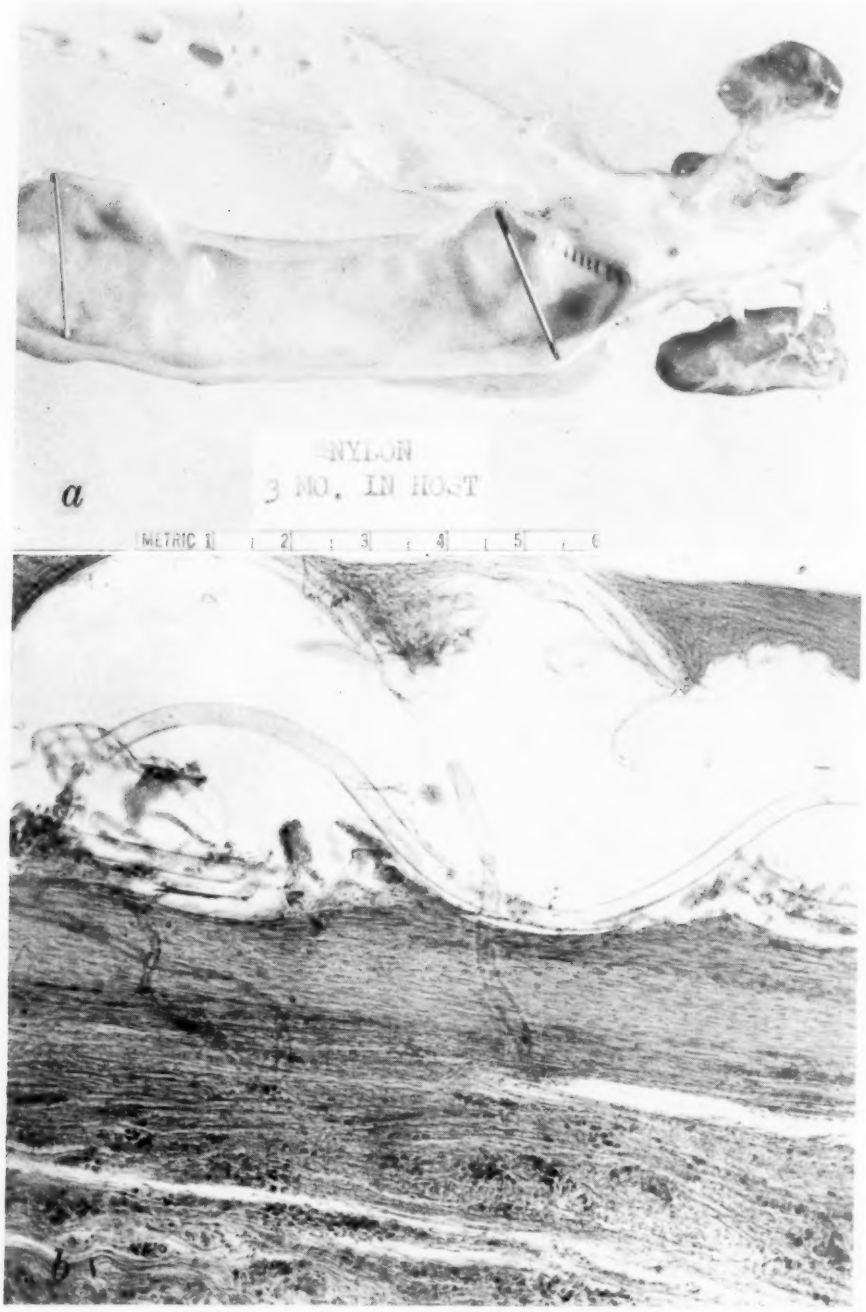

Fig. 5.—*a*, Distal portion of nylon prosthesis 3 months after implantation (host aorta above and to the right). Luminal surface covered by thin, well-organized fibrous layer. *b*, Photomicrograph (×70, reduced ½) of same specimen. Intact intimal surface and orderly periprosthetic connective tissue growth which is fairly abundant but not excessive.

partially occluded by mural thrombi at the site of some moderate to marked wrinkling; the remaining portions of the implants in these cases were in

good condition. The prosthesis in the dog dead of empyema at 2 weeks was in every way satisfactory. The prostheses recovered by sacrifice (5) were satisfactory, but 4 contained minor defects such as small fibrin deposits on

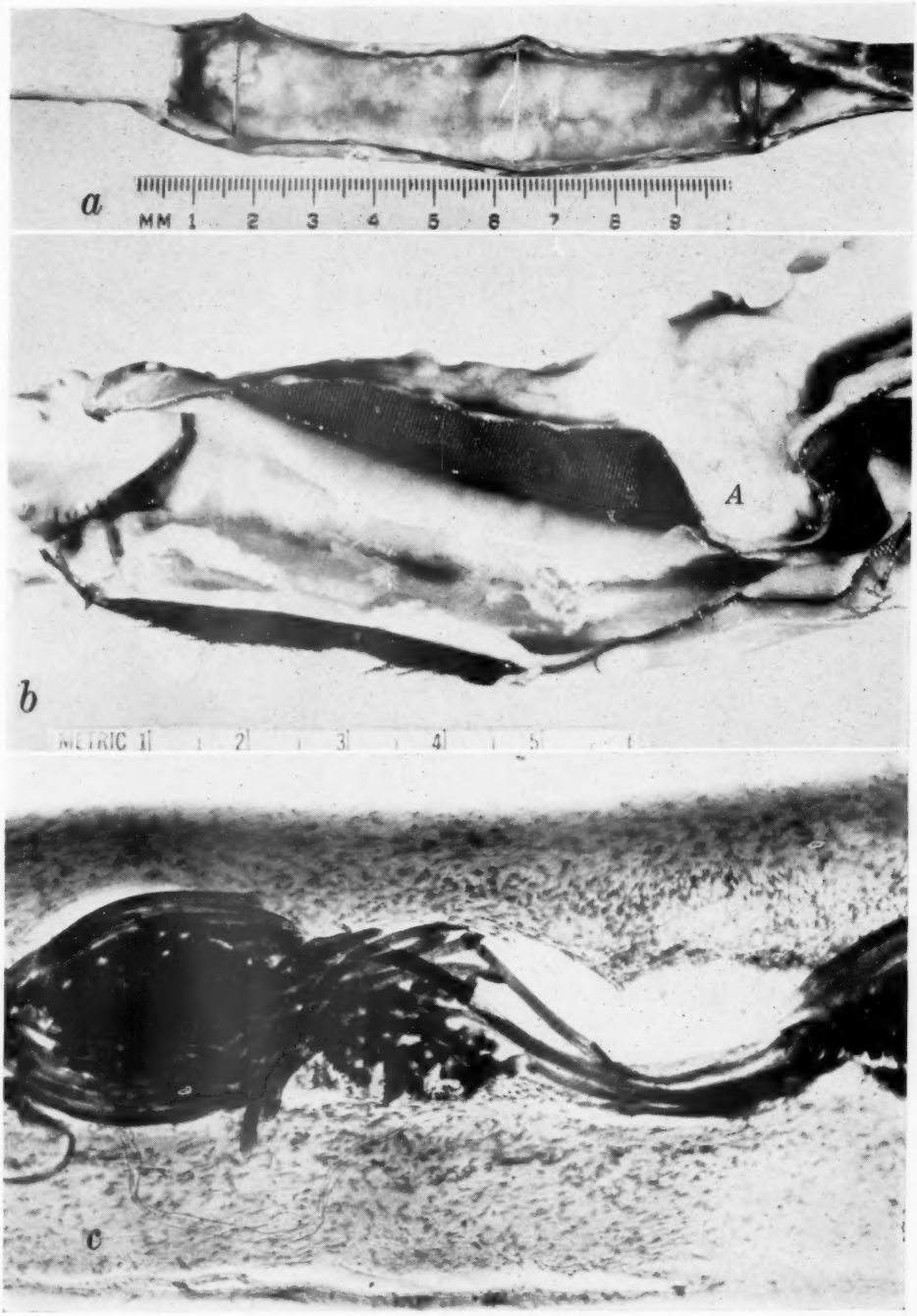

Fig. 6.—*a*, Proximal portion of unbleached teflon prosthesis 4 months after implantation. Orderly luminal and adventitial ingrowth of connective tissue. *b*, Caudal portion of an unbleached teflon prosthesis at 38 days, occluded at *A* by a clot formed at a point of marked wrinkling (host aorta to the left). *c*, Photomicrograph of specimen in *a*. Smooth luminal surface. The periprosthetic connective tissue reaction is less abundant than that seen in Fig. 5, *b*. (Note: Since teflon fabric is hard to section, the tissue preparation of specimens containing teflon must be thick; hence cellular detail is less distinct.)

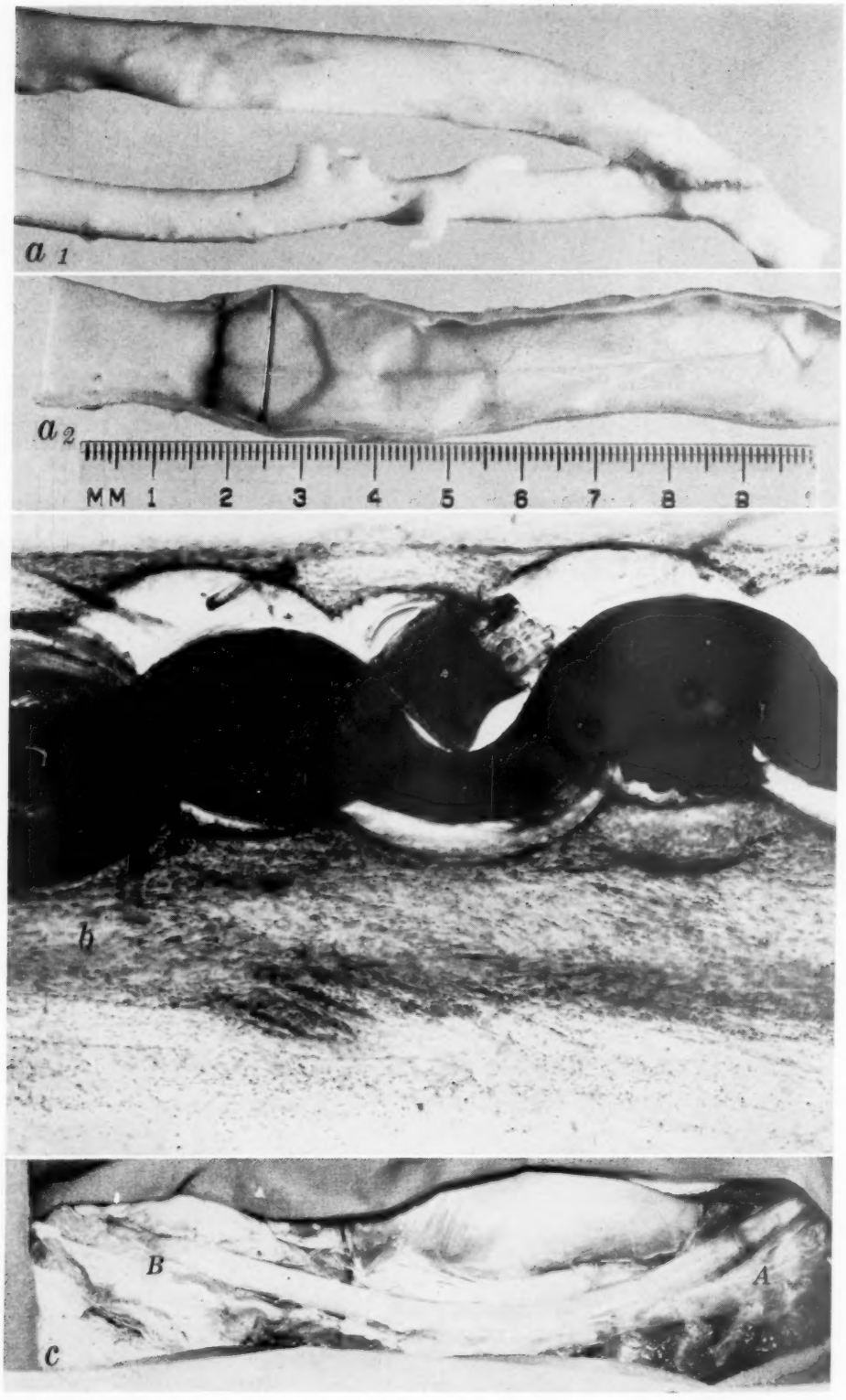

Fig. 7.—a_1, Caudal portion of bleached teflon prosthesis 6 months after implantation (host aorta at bottom); a_2, the proximal portion of the same specimen opened. Smooth unbroken luminal surface and orderly ingrowth of periprosthetic connective tissue. *b*, Photomicrograph of bleached teflon prosthesis 4 months after implantation. Both the luminal and adventitial layers of connective tissue ingrowth are well organized and of optimal amount. *c*, The gross appearance in situ of a bleached teflon prosthesis 6 months after implantation. A pliable, firm vascular tube has been formed, almost indistinguishable from the host aorta, that lies in a bed of tissue of minimal fibroblastic and leukocytic reaction (*A*, proximal, *B*, distal suture line).

the luminal surface in areas of slight wrinkling which were not endothelialized. In all these prostheses, by far the largest portion of the luminal surface was covered with a thin fibrous tissue giving the exact appearance of endothelium. The tissue reaction in the periprosthetic layer was either very mild or only moderate. Microscopic sections confirmed the lack of tissue reaction of important degree surrounding the teflon inserts.

Bleached Teflon.—Of the 10 dogs in this group (Table VI, Fig. 7, *a-c*) 6 were sacrificed on schedule, 3 dogs are living and well at 6 months, and one animal expired at 3 weeks of undetermined cause. In all these instances the prostheses were functioning well. The luminal surfaces were covered with a thin layer of organized fibrin which on microscopic examination was seen to be lined by flat, endothelium-like cells. A thin layer of well-organized fibrous tissue surrounded the implant, which was well attached to the interstices of the fabric and which created the impression of a well-formed vascular tube. This tube could be easily dissected out in an intact form. Two prostheses showed slight wrinkling without appreciable thrombosis, and in 4 prostheses minute fibrin deposits were present. The microscopic examinations, in addition to the finding in the intima already mentioned, confirmed the lack of host tissue reaction in the periprosthetic region (Fig. 7, *b*).

DISCUSSION

Choice of Experimental Method.—A correctly conceived animal experiment aimed at the study of human arterial replacement should, of course, reproduce with the greatest possible fidelity the anatomic and physiologic characteristics of the human arterial segment under investigation. The characteristics that one must take special pains to simulate are the dimensions (length and width), the anatomical environment, and the hemodynamic relationships of the arterial segment. The experimental reproduction of these characteristics of the human femoropopliteal arterial trunk poses considerable difficulties. Obviously, none of the laboratory animals the use of which is practically feasible possesses peripheral arteries strictly comparable to their human counterparts. The ileo-femoral arterial segment of the dog, in particular, was found unsuited for the purposes of the investigation both because of its limited length and because of its small diameter. By trial it was established that the use of the aortic by-pass described above would be the closest practical approximation to a replica of the human femoropopliteal trunk. The vascular pathway thus created has almost the same physical dimensions as the human femoral artery, and its spatial disposition is not significantly dissimilar. The hemodynamic correspondence is less complete since the intraluminal pressure of the by-pass, being that of the canine thoracic aorta, is higher than the human femoral arterial pressure. This last circumstance—other factors being equal—would, of course, tend to enhance the maintenance of patency in the by-pass, a fact that must be borne in mind in any possible clinical interpretation of the experimental results. In evaluating the experimental preparation, another aspect of the physiologic effects of the diversion of the thoracic aortic blood

through the by-pass must be mentioned, although it had no direct bearing on the fate of the vascular substitutes. The observation that some of the experimental animals developed various degrees of malnutrition and debility suggested that the retrograde flow by which the blood from the by-pass reached the abdominal viscera was of impaired effectiveness.

Since clinical experience has amply proved that homografts of the length and diameter here considered can be used with a high degree of success, the primary purpose of the experiments performed with homografts was not to test further this fact but rather to provide controls. The choice of homografts as controls seemed justified in view of the very extensive clinical and laboratory evidence that, for handling ease, versatility of usefulness, and excellence of over-all results, homografts, though far from ideal, are superior to all other arterial substitutes heretofore tested.

Heterografts.—The behavior of heterologous arterial transplants has been investigated fairly extensively in the past with results that have been reported as varying from very good to very bad.[2, 8, 9, 11, 18] Our observations fell into three distinct groups. In one group, considered satisfactory, the heterografts underwent a series of degenerative changes and connective tissue replacement not dissimilar to the events seen in the histologic evolution of homografts. Although the degenerative changes were more rapid and the connective tissue replacement somewhat less orderly than in homografts, there grafts appeared to serve their purpose, at least for the duration of the experiment. In the second group, the grafts showed evidence of rapid degenerative alterations without a concomitant process of connective tissue ingrowth. These grafts ruptured, usually in relatively short periods of time following implantation. In the third group, which may be regarded as an intermediate one, the progress of the degenerative changes was less rapid and it was accompanied by some irregular connective tissue reaction. Grafts in this group were characterized by aneurysmal dilatation, which is not compatible with a long period of functional usefulness.

The very wide variation in the donor-host reactions in heterologous grafts leads one to speculate whether the nature of the tissue reaction in any given case may not be determined by immunologic factors. This aspect of heterologous tissue transplantation urgently needs further elucidation. The marked variation of the behavior of heterologous grafts would also seem to suggest an explanation for the divergences in the results with these grafts reported in the literature. Obviously, when the range of variations in behavior is so wide, in a given short series of observations it is possible by chance to come across predominantly good results or results that are entirely unsatisfactory. However, the practical meaning of the results of both this series and those reported by others is clear: The performance of heterografts is entirely too unpredictable to allow their clinical application. The fact that a high proportion of the unsuccessful heterografts rupture would render their clinical use particularly hazardous.

Plastic Prostheses.—With respect to plastic prostheses, the main interest of this study lay in the investigation of the properties of teflon tubes. Although many plastic fabrics have in the past been reported as applicable to biologic and clinical purposes, we detected particularly promising qualities in the extreme durability, almost complete physiochemical inertness and nonwettability of teflon. Nylon was included in the study for two purposes: first, and more importantly, as the plastic most extensively investigated in biologic applications and one that has shown excellent properties in short-segment arterial replacement,[6, 10, 20, 21] it was chosen as a standard of comparison; at the same time its behavior in long-segment substitution, hitherto unreported, was also subjected to testing.

For several reasons the evaluation of the results of the study of plastic prostheses must be made not only in the conventional terms of rate of thrombosis but also on the basis of the histologic changes elicited by the implants. In general, the comparison of the experimental behavior of arterial substitutes on the sole basis of rate of thrombosis is subject to inaccuracy, since obviously the occurrence of thrombotic occlusion depends on many factors besides the type or composition of the substitute. Unless the size of the groups compared is large enough to cancel out the effects of these uncontrolled variables, the degree of success calculated on the basis of the rate of thrombosis alone may be incorrect. In the case of plastic prostheses an assessment of performance based solely on rate of thrombosis is particularly prone to error since even minor technical mistakes committed in implanting these substitutes may readily lead to thrombotic obliteration. Aside from the statistical pitfalls, it is desirable to take into account the comparative histologic reactivity of the various plastics also because their long-term fate most likely rests on the type of tissue changes they provoke in the operative site.

In the present series, with respect to rate of success based on incidence of thrombosis the various substitutes (excluding heterografts) ranked in the following order: bleached teflon, homograft, teflon, and nylon. (It should be pointed out that even the lowest rate of success, that of nylon [70 per cent], was of the order that would be regarded as acceptable, though not excellent, in terms of clinical experience.) However, the groups compared were small, and a scrutiny of the results shows that the incidence of thrombosis was more clearly related to technical imperfections—in the case of plastics, wrinkling*—than to the type of replacement. But whereas firm statistical conclusions as to performance solely in accordance with the incidence of thrombosis does not seem warranted, the comparison of the tissue changes elicited by the prostheses offers a more reliable basis for the assessment of their relative value. These changes were quite uniform within any given group and gradations could be seen from one group to another. While all plastics revealed excellent qualities of tissue reactivity, bleached teflon showed a clear superiority, thus occupying

*Wrinkling of plastic prostheses is the direct result of their nonyielding inelastic character. All presently available plastic woven tubes lack elasticity, and when they are used to replace arterial segments of over 10 to 15 cm. in length even small deviations from the precise length of the segment to be replaced may lead to slackness and kinking which in turn almost always leads to gradual thrombotic occlusion. A similar circumstance pertains when the prosthesis is laid over a joint, where it may be bent during movement.

in this respect the same relative position as it did in regard to rate of thrombosis. The bleached teflon prosthesis in 4 to 6 months after implantation resulted in a vascular tube grossly almost indistinguishable from the host aorta, and microscopically made up of a well-organized exudate-free, firm but thin connective tissue sheath infolding the fabric which on the luminal surface was covered with a smooth pseudo-intima.

As formerly mentioned, one of the most valuable physical properties of teflon as biologic implant material appears to be its durability, i.e., its resistance to mechanical wear and tear. Coupled with its chemical inertness, this property promises to assure the physical integrity of the implanted teflon prosthesis for long periods of time, and undoubtedly long enough to permit, without losing its tensile strength, the full histologic development of the new vascular tube. It should be pointed out, however, that the studies here reported do not give final proof for this assumption, and that observation of the implants extending over at least two years, and preferably more, will be needed before definitive judgment can be reached.

SUMMARY AND CONCLUSIONS

1. Segments, 18 to 24 cm. long and 8 to 10 mm. in diameter, of lyophilized, chemically sterilized bovine heterograft, and of seamless woven tubes of teflon, bleached teflon, and nylon were implanted in dogs and observed for periods of from 2 weeks to 13 months.

2. The heterografts showed a varying and capricious behavior, about one-half of the implants yielding satisfactory results, about one-third rupturing, and the remainder undergoing moderate to advanced degenerative changes.

3. During the periods of observation, prostheses of nylon, teflon, and bleached teflon of the stated dimensions proved to be satisfactory arterial substitutes. The few failures observed with these replacements appeared to be caused not by the unfavorable biologic behavior of the given plastic but rather by minor and virtually unavoidable technical errors that resulted in various degrees of wrinkling. Thus the importance of the lack of elasticity of these plastic prostheses that render the accuracy of their insertion a critical factor is again emphasized. On account of the minimal tissue reaction it elicits, as well as owing to its nonwettable and durable qualities, the seamless teflon prosthesis offers distinct advantages as a vascular substitute.

We wish to express our gratitude to Mr. John B. Sidebotham of John Sidebotham, Inc. (Frankford-Philadelphia, Pennsylvania) for supplying us the seamless woven tubing of teflon and nylon, and to Mr. Harry A. Burnett, Jr., for allowing us to use the extensive freeze-drying facilities of Difco Laboratories, Inc. (Detroit, Michigan).

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CENTRAL AND PERIPHERAL ARTERIAL PRESSURE PULSES

A Quantitative Study in Dogs With Normal and Incompetent Aortic Valves

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CENTRAL and peripheral arterial pressure pulses have been the subject of study for many years. Hurthle, in 1890,[8] and Frank, in 1905[5] were among the first to call attention to the variations in pulse pressure in different parts of the arterial tree. Since then, much has been learned regarding the central aortic pulse form, its genesis, and the changes in peripheral regions of the aortic system. This study was undertaken to examine quantitatively central and peripheral aortic pressure pulses in animals. Normal dogs and dogs with acute and chronic aortic regurgitation of graded severity were used.

METHODS

A technique has been described[10] for the controlled production of aortic insufficiency in dogs. It consists of the removal of a disc of tissue of known diameter from the base of one or more aortic leaflets. This is accomplished by means of an aortic leaflet punch. The free edge of the cusp is left intact. Varying degrees of aortic incompetence can thus be produced, depending upon the cardiac output of the dog and the amount of cusp tissue removed. A few animals with combined aortic and mitral insufficiency were also studied. Mitral insufficiency was produced by the transventricular severance of chordae tendineae as described by Haller and Morrow.[6]

Retrograde aortic catheterization was performed to determine pulse pressure changes in the aortic system. Dogs weighing 6 to 16 Kg. were anesthetized with Pentothal sodium and placed in the supine position. Two No. 7 Cournand cardiac catheters (capacity 1.2 c.c.; 100 cm. in length) were connected to a single Statham P23A transducer by a three-way stopcock; the transducer was connected to a suitable amplifier and direct recorder. The natural frequency of this system is approximately 18 cycles per second. The transducers were leveled 7 cm. anterior to the skin over the dorsal spine. One catheter was inserted into the femoral artery and secured with a ligature. The other catheter was introduced into the aorta via the contralateral femoral artery and through the aortic valve into the left ventricle. The catheter was then slowly withdrawn until the tip lay in the ascending aorta, just above the aortic valve. This position was evidenced by the change from a ventricular to an aortic pulse contour. Pressures were then recorded from the central aorta and femoral artery. Systolic, diastolic, and electrically integrated mean pressures were determined from each catheter in immediate succession. Each catheter was frequently irrigated with normal saline solution through another stopcock. In several experiments, the central catheter was withdrawn distally for measured distances and end pressures recorded at several points in the aorta.

Five of the dogs studied had normal aortic valves; in four of these (6N, 7N, 26N, 29N), moderately severe aortic insufficiency was produced immediately after aortic catheterization. After closure of the chest, catheterization was repeated in these dogs

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with acute aortic insufficiency (6AI, 7AI, 26AI, 29AI). Four dogs had chronic aortic insufficiency of varying severity (C1, C3, D2, J21), and three had combined chronic aortic and mitral insufficiency (NN, HO, CK).

RESULTS

Sixteen aortic catheterizations were performed in twelve dogs. Table I summarizes the results in these animals. Fig. 1 demonstrates the difference in systolic and diastolic pressure between the central aorta and femoral artery of a normal dog. Determinations of mean aortic pressure revealed no measurable difference between the central aorta and femoral artery in any dog studied.

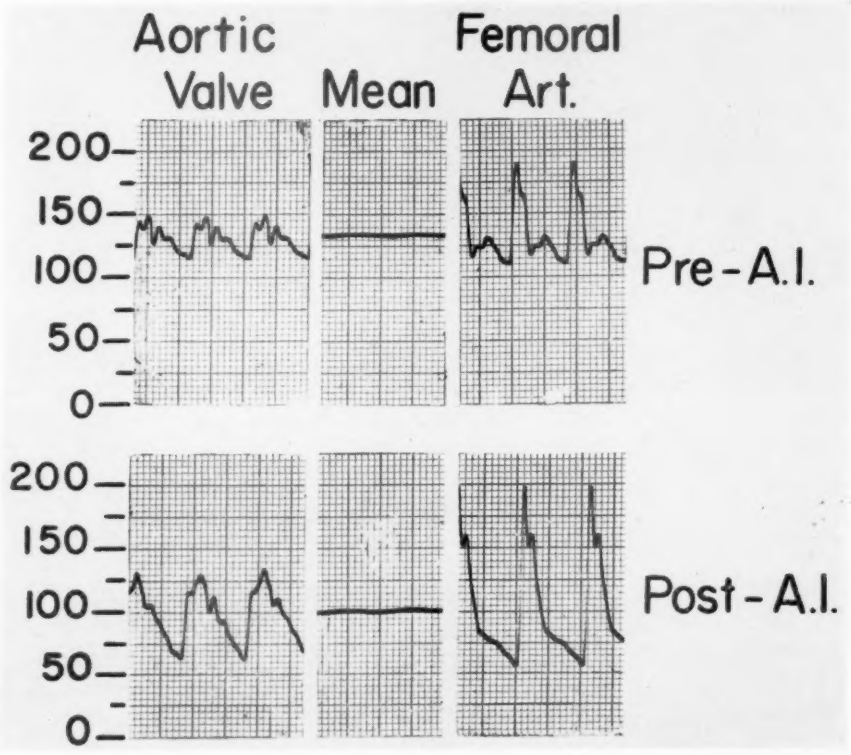

Fig. 1.—Central and femoral arterial pressure pulses and mean pressures of Dog 26 taken immediately before and after the production of aortic insufficiency. Scale in millimeters of mercury; paper speed 25 mm. per second.

Fig. 2 shows the exaggeration of this difference in a dog with severe chronic aortic insufficiency. Pressure pulses recorded at measured distances from the aortic valve illustrate the qualitative and quantitative changes which occur as the transmitted pulse wave is propagated along the aorta. The most striking and consistent change was progressive increase of the pulse pressure. In all of the dogs studied, this increase was due primarily to the augmentation of the systolic pressure. The increase in systolic pressure from the aortic valve to the femoral artery was 30 to 42 mm. Hg in normal dogs, 48 to 86 mm. Hg in dogs with aortic regurgitation, and 40 to 60 mm. Hg in dogs with combined aortic and mitral incompetence. A decline in diastolic pressure contributed to a lesser degree in the widening of the pulse pressure. Differences between

central diastolic and femoral diastolic pressure were 5 to 8 mm. Hg in normal dogs, 8 to 15 mm. Hg in acute aortic regurgitation, 15 to 30 mm. Hg in chronic aortic regurgitation, and 5 to 10 mm. Hg in combined aortic and mitral incompetence. The femoral pulse pressure was approximately double the central pulse pressure in both normal dogs and dogs with aortic insufficiency. The ratio was 2.0 to 2.4 with an average of 2.2.

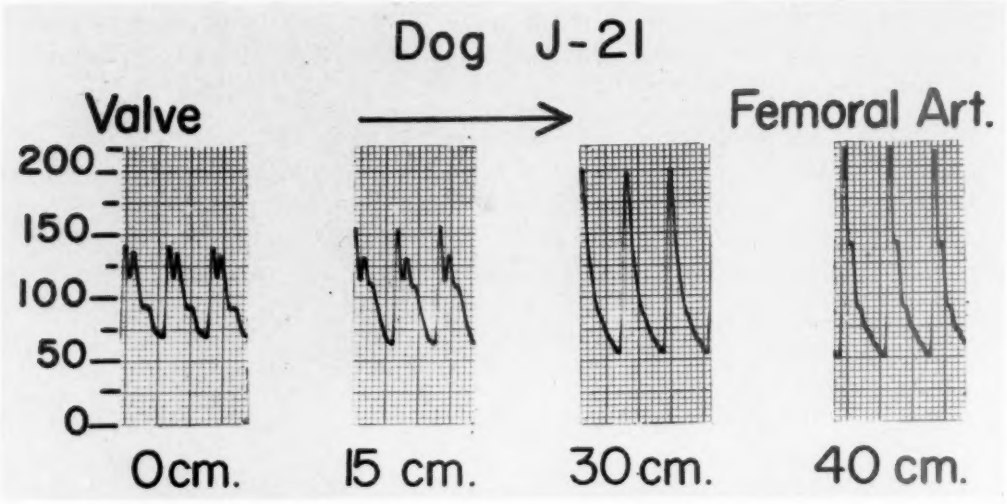

Fig. 2.—Aortic pressure pulses at aortic valve, femoral artery, and two points in the aorta in a dog with severe chronic aortic insufficiency. Scale in millimeters of mercury; paper speed 25 mm. per second.

TABLE I. ANALYSIS OF SIXTEEN AORTIC CATHETERIZATIONS

DOG NUMBER	SIZE OF LESION (MM. DIAMETER)	DAYS DURATION OF LESION	BLOOD PRESSURE			SYSTOLIC STEP-UP (MM. HG)	DIASTOLIC FALL (MM. HG)	FEMORAL/CENTRAL PULSE PRESSURE RATIO
			AORTIC VALVE	FEMORAL ARTERY	MEAN			
R-15	Normal		154/120	190/115	135	36	5	2.2
26N	Normal		150/115	190/110	132	40	5	2.3
26AI	4.9	<1	130/63	200/55	100	70	8	2.2
6N	Normal		158/110	200/105	130	42	5	2.0
6AI	3.9	<1	160/72	240/60	105	80	12	2.0
7N	Normal		140/110	170/102	129	30	8	2.3
7AI	3.9	<1	147/66	229/56	98	82	10	2.1
29N	Normal		157/117	190/110	135	33	7	2.0
29AI	4.9	<1	140/65	195/50	95	55	15	2.0
C-1	3.9	59	160/97	208/82	123	48	15	2.0
C-3	3.9 × 2	58	187/89	273/59	125	86	30	2.1
D-2	3.9 × 2	50	167/84	230/63	120	63	21	2.0
J-21	4.9 × 2	35	140/70	215/50	100	80	20	2.4
NN*	3.9	140	185/130	245/120	155	60	10	2.3
HO*	3.9	149	185/145	225/140	155	40	5	2.1
CK*	3.9	175	158/110	215/105	140	57	5	2.3

*Combined aortic and mitral insufficiency.

DISCUSSION

The mechanisms responsible for the different pulse pressures in the aortic system have been the subject of speculation for fifty years. In 1905, Frank[5] made a significant contribution by observing, in dogs, a higher systolic pressure in the femoral artery than in more central vessels. He attributed the difference to "reflections" in the aortic system and reasoned that the pressure pulses were altered by them. In 1924, Bazett[4] observed higher pulse pressures peripherally in dogs with aortic insufficiency and pointed out that the "differential" pressure in favor of the femoral was merely an exaggeration of a normal occurrence. In 1928, Wiggers[11] postulated that reflected waves may increase the amplitude of the fundamental transmitted wave by resonating with it. Hamilton and Dow[7] first studied end pressures in the aorta of the normal dog by means of a cannula introduced into the femoral artery. They proposed a standing wave theory to explain the changes in contour and pressure: "By reflection of the propagated wave . . . certain components of it resonate and the standing waves so produced are superimposed upon the fundamental pulse form." More recently Alexander[1, 2] has defined the aortic standing wave in terms of its genesis. He feels that this wave originates because of the "lowered resistance associated with the origin of the major splanchnic vessels at the level of the diaphragm and the increase in resistance at the femoral bed." Noble[9] is of the opinion that many reflected waves of varying wave lengths resonate with the transmitted wave to account for the qualitative and quantitative changes in aortic pressure pulses.

The present study has confirmed the increase in pulse pressure in the peripheral aortic system; this is due mainly to a rise in systolic pressure accompanied by a smaller decline in diastolic pressure. It is also apparent that the wide pulse pressures seen in aortic insufficiency are merely an exaggeration of the normal, and are of central origin. Aortic insufficiency results in an increased left ventricular stroke volume. This increase is greater in chronic aortic regurgitation than in acute incompetence. The changes tended to be less in dogs with combined aortic and mitral insufficiency since here the effective left ventricular stroke volume is presumably diminished by the mitral lesion. As can be seen from Table I, the ratio of femoral to central pulse pressure remained constant for a given animal before and after aortic insufficiency was produced. Alexander[3] noted no increase in this ratio after aortic insufficiency. Preliminary studies in patients indicate the femoral/central pulse pressure ratio is *increased* in the presence of aortic insufficiency.

Hamilton and Dow[7] using normal dogs, observed no differences in mean pressure between the aortic arch and various peripheral points; they also failed to observe any differences in diastolic pressure. Wiggers[12] suggests that mean pressure in the aortic system declines slightly in the periphery. The present study indicates that if there is a fall in mean pressure peripherally it is of small magnitude and was not detected by the techniques employed. This suggests that energy losses during the transmission of the aortic pulse wave from the valve to the femoral artery are small.

In the absence of a detectable difference in mean pressure between the aortic valve and femoral artery, the seeming paradox of higher systolic pressure

peripherally is made rational by Wiggers.[13] The pressure peak is reached later in the peripheral than in the central vessel, and aortic pressure exceeds femoral pressure during the early portion of systole. A reverse pressure gradient temporarily supervenes during the latter part of systole, allowing the momentary backflow of blood toward the aortic valve.

In a résumé of previous observations, Wiggers[14] concluded that the mean arterial pressure changed very little, if at all, in experimental aortic insufficiency. In contrast, it has been noted previously[10] and in the present study (Table I, Fig. 1) that both mean pressure and diastolic pressure fall significantly in acute aortic insufficiency.

SUMMARY AND CONCLUSIONS

Aortic pressure pulses were recorded centrally and peripherally in dogs with normal and incompetent aortic valves and in dogs with combined aortic and mitral insufficiency. Peripheral systolic pressure was 30 to 42 mm. Hg higher than central systolic pressure in normal dogs; peripheral diastolic pressure was 5 to 8 mm. Hg lower than central diastolic pressure. This systolic rise and diastolic fall was doubled in dogs with aortic insufficiency but the ratio of femoral to central pulse pressure (2.2) was unchanged. The wide peripheral and central pulse pressure in aortic insufficiency is an exaggeration of a normal finding and of central origin. There was no measurable difference between the mean pressures recorded at the aortic valve and the femoral artery.

Mr. William Laughlin rendered valuable technical assistance.

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PORTAL HYPERTENSION WITH HEMORRHAGE FROM ESOPHAGEAL VARICES SECONDARY TO ACUTE RECURRENT PANCREATITIS

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OUR interest in acute pancreatitis and its complications was recently stimulated by an unusual case on the Surgery Service at Minneapolis General Hospital. Portal hypertension with hemorrhage from esophageal varices as a result of acute recurrent pancreatitis has not to our knowledge been previously reported in the literature.

CASE REPORT

This is the case of a 55-year-old white man, hospital No. 80109, who was admitted to Minneapolis General Hospital for the first time on Aug. 25, 1954. He was referred by his private physician because of chronic alcoholism, with a bleeding peptic ulcer, and with a history of surgical drainage of a left subphrenic abscess on June 29, 1954.

Examination showed a normally developed, fairly well-nourished white man in semicoma, with a rectal temperature of 38° C., pulse of 120 per minute, respirations 48 per minute, and blood pressure 120/70 mm. Hg. The skin and mucous membranes were pale. The tongue was red and dry. There were moist râles over both lower lung fields. Bilateral subcostal surgical scars were present, with a sinus in the left scar from which a small amount of purulent drainage exuded. There was no irritation of the skin. Bowel sounds were hypoactive. An ill-defined mass was palpated extending 10 cm. below the left costal margin. Normal brown stool was present in the rectum. The patient occasionally roused to give slurred, confused responses to questions.

During the examination the patient vomited approximately 2,000 c.c. of coffee-ground material. Continuous gastric suction yielded 800 c.c. of the same material. A unit of whole blood was given rapidly and the patient's clinical appearance improved.

Emergency laboratory data were: Hemoglobin 8.8 grams per cent; hematocrit 29 volumes per cent; leukocytes 16,600 per cubic millimeter with 85 per cent neutrophils; urine 4-plus sugar with a specific gravity of 1.027. The blood sugar was 656 mg. per cent, CO_2 combining power 39 meq. per L., chloride 83 meq. per L., and serum amylase 434 Somogyi activity units.

Serial blood volume determinations by the Evans-Blue technique were used as a basis for blood replacement and the patient received 2,900 c.c. of whole blood in the first twenty-four hours. Five per cent dextrose in distilled water covered by 20 units of regular insulin per liter was given intravenously in addition.

A composite picture of his medical history was gained later through several sources. This included:

1. Private hospitalization for four days in March, 1953, with a discharge diagnosis of subacute cholecystitis. The leukocyte count was 26,150 per cubic millimeter with 95 per cent neutrophils. No amylase determination was done. Urine was positive for sugar.

2. Private hospitalization in August, 1953, for elective cholecystectomy. Pathologic report was "subacute cholecystitis."

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3. Private hospitalization from May 27, 1954 to Aug. 5, 1954, for acute abdominal pain, vomiting, and shock. Serum amylase was 1000 activity units. Norepinephrine was required for several days. On July 7, melena and hematemesis were noted. Barium enema was negative. Upper gastrointestinal x-ray study showed narrowing of the antrum but no mucosal changes. The duodenum was normal. Chest x-ray, on July 13, revealed atelectasis with fluid at the base of the left lung. Two weeks later left upper quadrant tenderness and mass were discovered. Surgical drainage of a "grapefruit-sized mass in the region of the mesocolon, superior to the pancreas and lateral to the stomach" was effected.

4. Coffee-ground emeses occurred on several occasions following discharge in August, 1954, accompanied by confusion and disorientation. During one of these periods, he pulled out the drainage tubes from his left upper quadrant wound.

For the first three days after admission to the Minneapolis General Hospital, the patient experienced frequent periods of confusion. The temperature ranged from 38.1° C. to 39.4° C., rectally. Chest x-rays revealed extensive bilateral bronchopneumonia. On August 27, the hemoglobin was 14.2 grams per cent and hematocrit 41 volumes per cent. Serum amylase dropped to 72 activity units. On August 29, a large amount of purulent material drained from the abdominal sinus. Coagulase positive *Micrococcus pyogenes* (*var. aureus*), and *Proteus vulgaris* were isolated.

A massive hematemesis of coffee-ground material and fresh red blood occurred on August 30. With this episode, esophageal varices were suspected in spite of the referring physician's statement that peptic ulcer had been demonstrated radiographically. From September 1 to September 9, several lesser hematemeses occurred, requiring repeated transfusions. On September 3, barium study showed esophageal varices and moderate obstruction to the outlet of the stomach. A Sengstaken tube was emplaced and left for three days. Within twelve hours of its removal, bleeding again occurred requiring reinstitution of tamponade.

Laboratory results during this period included a prothrombin time of 21.4 seconds with a control of 13.8 seconds. Bilirubin was 0.15 mg. per cent in one minute and 0.95 mg. per cent total. This rose to 2.0 mg. per cent in one minute and 5.3 mg. per cent total on September 9. Cephalin-cholesterol was 2 plus in 48 hours, thymol turbidity 16.5 units. The albumin-globulin ratio was 2.90/3.50 grams per cent. Alkaline phosphatase rose from 34.6 King-Armstrong units on September 1 to 78.3 on September 9. Amylase levels remained below 50 activity units.

Another attempt at discontinuation of the Sengstaken tube was followed by more hematemeses. A shunting procedure was then contemplated as a definitive measure. However, it was felt that an attempt at correction of the bilirubin, albumin-globulin levels, and the prothrombin time should precede surgery of this magnitude. Gastric dilatation developed on September 13 and suction returned 1,500 c.c. of gastric content. Hematemesis of coffee-ground material occurred that evening necessitating replacement of the Sengstaken tube. X-ray study indicated nearly complete pyloric obstruction.

Emergency laparotomy was performed on September 14, disclosing: (1) an indurated mass involving the head and neck of the pancreas and second portion of the duodenum; (2) generalized distention of mesenteric veins, gastro-epiploic venous pressure was 250 mm. of water measured from the anterior surface of the body of the second lumbar vertebra, and the portal vein was normal to palpation; (3) the abdominal sinus extended into the retroperitoneal space in the left upper quadrant but no abscess was detected; (4) the liver was grossly normal, liver biopsy was taken (microscopic examination showed no evidence of cholangitis or cirrhosis); and (5) antrotomy with intraduodenal digital examination revealed almost complete obstruction of the second portion of the duodenum; annular pancreas could not be demonstrated.

Antecolic gastrojejunostomy was performed. The patient withstood the procedure well and had an excellent postoperative course.

The incision healed without complication. Subjective improvement was dramatic. Liver profile studies showed gradual return to normal levels except for the alkaline phos-

phatase which remained around 70 to 90 King-Armstrong units for about two months. Ten days after surgery, upper gastrointestinal x-ray study demonstrated a well-functioning gastroenterostomy and the esophageal varices were much less prominent. Thirteen days after surgery, esophagoscopy revealed "mild esophagitis of the distal esophagus but no visible varices."

The patient's improvement continued until the development of manifest diabetes mellitus three months later. This was satisfactorily controlled with 55 units of NPH insulin daily. Following this he regained his normal weight and resumed his regular employment as a parking-lot attendant.

DISCUSSION

The major complications in this case of acute pancreatitis include: (1) abscess, or pseudocyst formation; (2) duodenal obstruction; (3) portal hypertension with bleeding esophageal varices; and (4) diabetes mellitus. These complications are not common, but the only one which has not received attention in the literature is the bleeding varices.

The findings in our case strongly support the development of a portal hypertension secondary to acute recurrent pancreatitis, with subsequent hemorrhage from esophageal varices. The evidence favoring this is: (1) the massive upper gastrointestinal hemorrhage which was repeatedly arrested by esophageal tamponade; (2) radiologic demonstration of esophageal varices before surgery; (3) dilated portal bed and elevated portal pressure demonstrated at laparotomy; (4) extreme induration about the head of the pancreas; (5) biopsy of the liver showing no cirrhosis; and (6) the esophageal varices regressed as shown by x-ray and esophagoscopy. No further hemorrhage occurred postoperatively.

No reference to hemorrhage from esophageal varices secondary to acute pancreatitis was found in a review of the literature for the past five years, with some attention also given earlier writings. Paxton studied 800 cases of proved acute pancreatitis and found gastrointestinal bleeding from superficial ulcers of the stomach, duodenum, small intestine, and colon. In his experience acute pancreatitis is fairly common in alcoholics with cirrhosis, but gastrointestinal hemorrhage associated with their attacks was not seen.[5, 6] Doubilet[2] refers to hemorrhage from submucosal varices resulting from localized obstruction of small portal tributaries by dense pancreatic fibrosis. He also attributes hemorrhage to duodenitis and gastritis caused by the adjacent pancreatic inflammatory reaction. Gambill and his associates[3] report a case with bleeding from two deep gastric ulcers of the anterior wall, associated with a fatal case of acute pancreatitis. Brown and Smiley[1] had a case of acute pancreatitis secondary to mumps in a 64-year-old man who developed melena and hematemesis. At laparotomy a normal liver and spleen were found; subtotal gastrectomy disclosed patchy shedding of the surface epithelium. Two cases of mesenteric vascular occlusion following pancreatitis are reported.

The cause of esophageal varices is usually recorded as elevation of the portal venous pressure or portal hypertension. This may be due to intrahepatic obstruction to the portal blood flow as in the various types of cirrhosis, or to extrahepatic obstruction resulting from thrombosis of the portal vein. Rack and his co-workers[7] state that esophageal varices may occur in the absence

of disease of the liver or portal system and with a normal portal venous pressure. Gray and Whitesell[4] feel that in such cases the esophageal varices may at times have a primary origin in the azygos system.

Our case fits into the extrahepatic group in that the portal vein was obstructed outside the liver as a result of acute recurrent pancreatitis. We are of the opinion that the portal hypertension here was due to compression of the portal vein by the surrounding inflammatory process rather than to thrombosis in the portal venous system. This is attested to by a normal portal vein on palpation during laparotomy, and by the rapid disappearance of the esophageal varices with regression of the phlegmonous changes.

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CHEMODECTOMA OF THE GLOMUS INTRAVAGALE

Report of Two Cases: One With Regional Lymph Node Metastases

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CHEMODECTOMAS in the upper neck, usually arising from the carotid body or glomus jugulare, have been reported with increasing frequency in recent years. These tumors, known also as nonchromaffin paragangliomas, carotid-bodylike tumors, and receptomas, have been recognized in the aortic bodies ("glomus aorticum," Lattes[28]), the region of the ganglion nodosum of the vagus nerve ("glomus intravagale," Lattes[28]), and in the orbit as well ("paraganglion ciliare," Fisher and Hazard[13]).

To our knowledge, the cases which we are reporting represent the eighth and ninth recorded chemodectomas, or nonchromaffin paragangliomas, arising in the glomus intravagale, and our second case is the first such tumor observed with regional lymph node metastases, although widespread bony metastases from this tumor were reported by Burman, in 1955.[7]

The clinical symptoms in these cases and their possible relationship to chemoreceptor activity and vagal dysfunction were of such interest that a detailed report appeared indicated. Of equal significance were the surgical anatomic relationships of these tumors.

REPORT OF CASES

Case 1.—R. E. R. (106631), a 47-year-old white male veteran, was admitted July 7, 1952, for treatment of a mass appearing from beneath the left angle of the mandible. In addition to this mass, he complained of a group of symptoms which had their inception in 1941 while he was in the military service. These consisted of fatigue, a sense of disturbed balance, blurred vision, loss of ability to maintain pace and rhythm while marching, persistent soreness in the left side of the throat, shortness of breath on exertion, dizzy spells, and loss of mental concentration. After protracted hospitalization and thorough examination he was discharged from the military service with a diagnosis of neurasthenia. After returning to civilian life, his symptoms continued unabated. In early 1942, he developed cramping epigastric pain and diarrhea. The epigastric cramps occurred about one hour after eating and were accompanied by sweating and occasionally by vomiting. These symptoms progressed, and in January, 1943, a gastroenterostomy was performed at another hospital because of gastric retention. Abdominal cramps were relieved. About this time the patient first noted a small mass in his left upper neck beneath the angle of the mandible. The general symptoms continued and he noted an abnormal sensitivity to cold. In 1946, an appendectomy was performed because of vague abdominal symptoms and in the same year thyroidectomy was performed because of persistent nervousness. In April, 1948, an attack of vertigo was diagnosed as Menière's disease. In December, 1948, a second severe attack of vertigo with inability to stand occurred. At this time ringing

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in the left ear appeared and persisted until the time of admission. By 1950, the cervical mass had reached a size which occasioned clinical interest. A needle biopsy was attempted but the operator obtained only blood. In September, 1950, the mass was explored at another hospital but was not removed because of severe bleeding. A biopsy was not taken and the patient was told that he had a carotid body tumor which was not removable. During the ensuing two years the patient was plagued by stumbling gait, lack of balance, nausea after eating, and increasing cardiac consciousness with a sense of palpitation. He was particularly distressed by the embarrassing occurrence of inability to board a street car because of "blacking out" after running to catch the car. This experience recurred several times. On admission, July 7, 1952, physical examination was normal except for the presence of scars of previous operations and the presence of a firm mass presenting from beneath the left angle of the mandible. This tumor could be palpated through the left pharyngeal wall with bimanual examination. The vocal cords moved normally. Roentgenograms of the skull and paranasal sinuses failed to reveal any evidence of bone erosion or any abnormality of the cranial foramina.

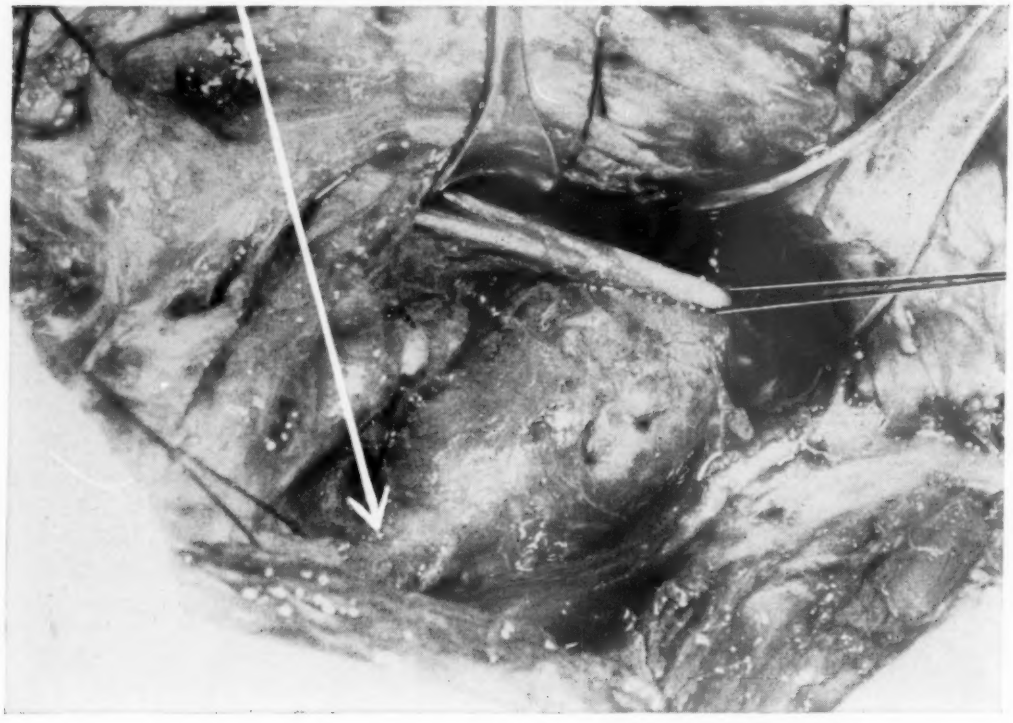

Fig. 1.—Operative field in Case 1. Arrow indicates the enlarged vagus nerve at the distal border of the tumor. The hypoglossal nerve is elevated by the ligature. Segments of the jugular and common facial veins have been resected.

Operation and Findings.—On July 14, 1952, the area of the tumor was re-explored by excision of the scar in the left submandibular crease. The deep cervical fascia was incised and the tail of the parotid was turned upward exposing the tumor. It lay beneath the internal jugular vein which crossed its outer surface. The common facial vein joined the jugular near the lower pole of the tumor. From the lower pole a cordlike structure, 4 mm. in diameter, extended downward into the neck (Fig. 1). The jugular and common facial veins were divided and ligated and a segment of each resected. After the anterior surface of the tumor was cleared from the scar of the previous operation, it could be removed with relative ease. There were several vessels, averaging 2 to 3 mm. in diameter, which entered it. As the dissection was carried upward, it was found that the tumor passed beneath the hypoglossal nerve (Fig. 2) and beneath the stylohyoid and posterior belly of the digastric muscle. The tumor was freed upward to the jugular foramen where

it terminated, and it became evident at this time that the lesion arose in the ganglion nodosum of the vagus nerve. The tumor was freed above and delivered and the vagus nerve was traced downward into the neck and divided at the lower border of the larynx where the nerve had assumed normal proportions. The tumor had invaded the nerve trunk for a distance of about 1 cm. (Fig. 3). During the operation, the anesthetist noted that manipulation of the tumor resulted in slowing of the pulse rate from 90 to 80 per minute and reduction of blood pressure from 100/70 to 70/55.

Postoperative Course.—Paralysis of the left vocal cord, which remained fixed in the mid-line, was immediately noted. There was a transient paralysis of the left hypoglossal nerve. Symmetrical protrusion of the tongue returned within three months. The patient's voice remained husky, but improved slightly in quality three months after operation, and

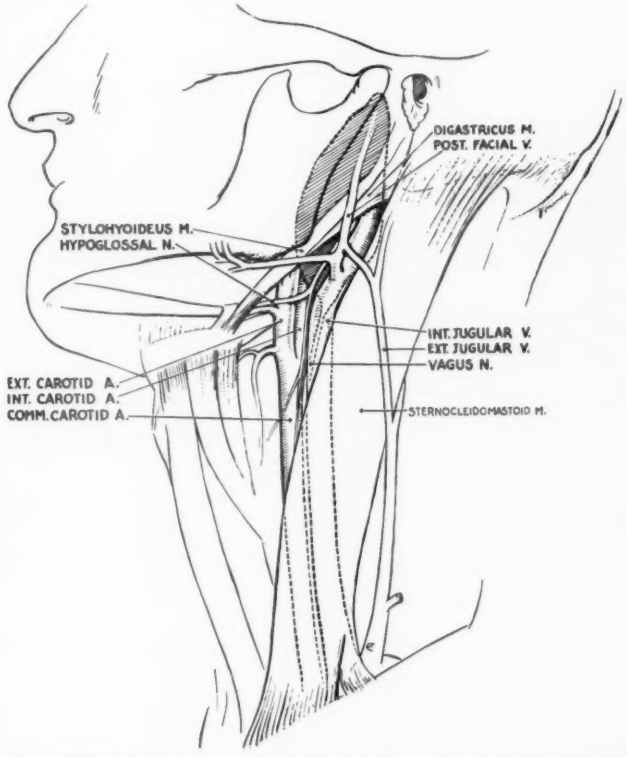

Fig. 2.—Diagram illustrating the anatomic relationships of ganglion nodosum tumors to the other structures in the neck.

the patient noted that he could speak with almost normal tone when recumbent. The systemic complaints were almost entirely relieved. Postprandial nausea, palpitation, and nervousness disappeared. Ability to concentrate attention and sense of rhythm returned, Tinnitus, however, persisted.

Pathologic Findings.—

Gross: The gross surgical specimen consisted of a 9.5 cm. segment of the left vagus nerve at the proximal extremity of which was a bulbous enlargement measuring 4.5 by 3 by 1.8 cm. The diameter of the vagus nerve at the distal line of resection was 0.4 cm. The mass was encased in a fibrous capsule the external surface of which was rough, ragged, and reddish gray. On cut section the tumor was fleshy, tannish pink, and spongy and bore a moderate resemblance to thyroid tissue. It was subdivided into irregular lobules by trabeculae of firm, gray, fibrillar tissue. The tumor weighed 10 Gm. after removal of the distal segment of the nerve (see Fig. 3).

Microscopic: The tumor was composed of nests or "Zellballen" of moderately large oval cells with medium-sized round or oval nuclei. The cells (which have been referred to as "chief" or "epithelioid" cells) were of fairly uniform size and had moderately abundant

Fig. 3.—Cut surface of the gross specimen removed from Case 1. Note the subdivision of the tumor into irregular lobules by narrow fibrous trabeculae and the extension of tumor down the first centimeter of the distal segment of the vagus nerve.

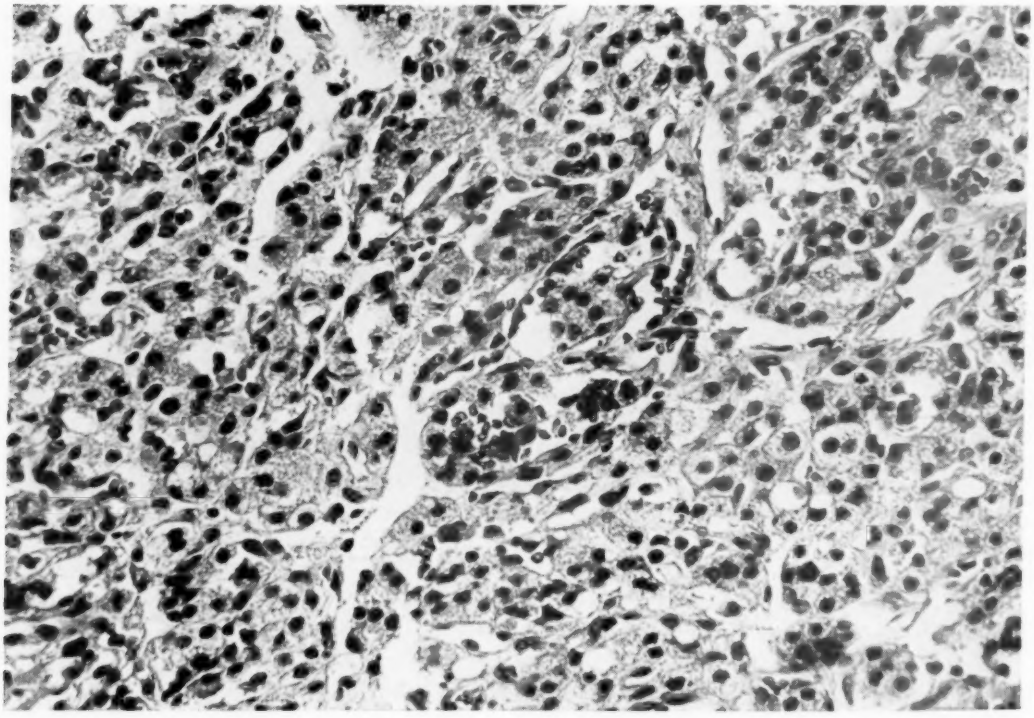

Fig. 4.—Representative field from Case 1 illustrating the characteristic histologic pattern of large "chief" or "epithelioid" cells arranged in nests of "Zellballen." This pattern was observed in both cases (×375; reduced ⅓).

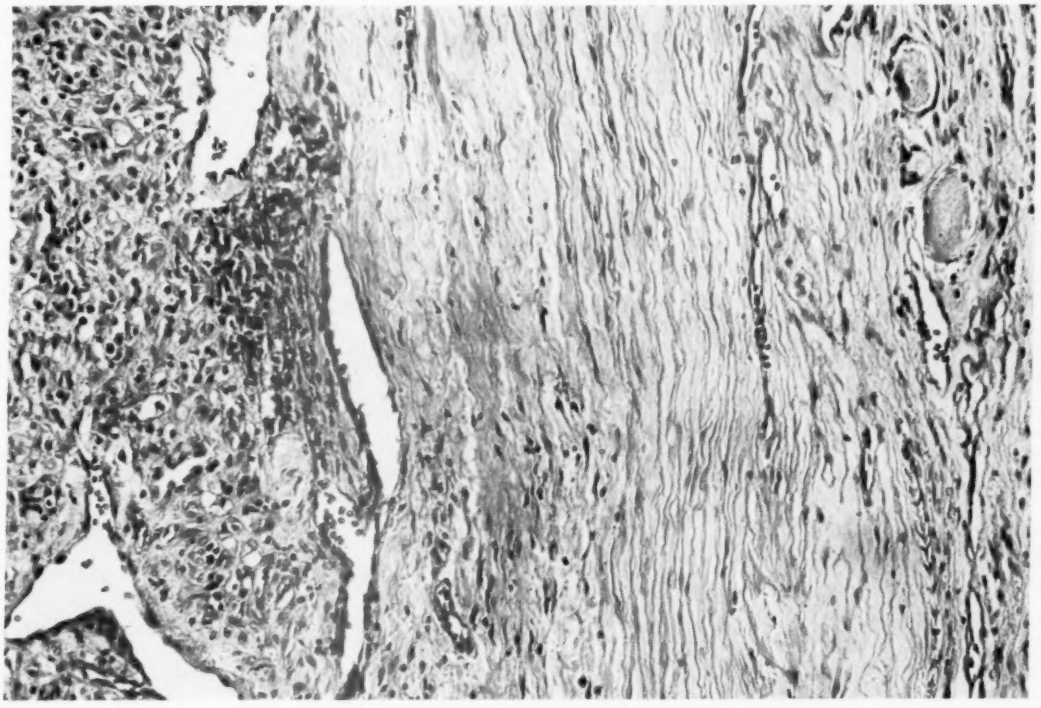

Fig. 5.—Ganglion cells and nerve fibers in the fibrous capsule of the tumor in Case 1 (×195; reduced ⅓).

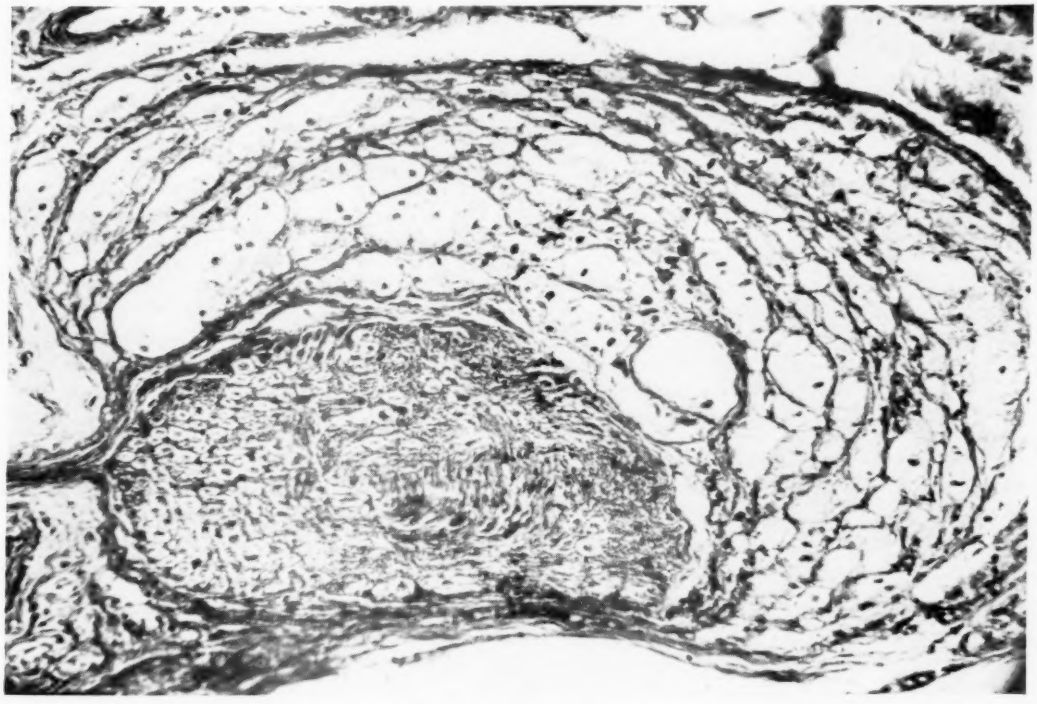

Fig. 6.—Holmes' stain of the vagus nerve at the distal border of the tumor in Case 1. Nerve fiber degeneration is absent although the nerve is partially encircled by tumor as indicated by the reticulum pattern outlined in the upper and right quadrants of this illustration (×75; reduced ⅓).

acidophilic fibrillar cytoplasm (Fig. 4). In a few areas, moderate variation in the size and staining quality of the tumor cells was observed. A few tumor giant cells and a few multinucleated cells were present. No mitoses were observed. The cell nests were surrounded by a delicate reticulum (Wilder's reticulum stain) arranged in the fundamental pattern of the carotid body and it tumors as emphasized by LeCompte.[30, 32] Between the cell nests ran numerous small capillaries. Fibrous septa containing numerous small blood vessels subdivided the tumor into irregular lobules. In the fibrous capsule, about the periphery of the mass, were clusters of large ganglion cells and bundles of nerve fibers indicating displacement of these structures of the ganglion nodosum by the growth (Fig. 5). Sections of the vagus nerve distal to the tumor stained with osmic acid and other preparations stained by Holmes' method (Fig. 6) showed no evidence of nerve fiber degeneration. This would indicate that the elements of the vagus in the region of the ganglion nodosum were not destroyed but only displaced by this neoplasm.

Chromaffin properties were absent from this tumor as indicated by staining the tissue by: (1) Schmorl's method modified by mordanting the formalin-fixed tissue in 5 per cent potassium dichromate for ninety-six hours, (2) Ogata's silver method modified by application to formalin-fixed tissue, and (3) Gömöri's method. Formalin-fixed adrenal medulla used as control tissue in each case gave positive chromaffin reactions.

CASE 2.—D. H. T. (107669), a 65-year-old, asthenic white man, was admitted on Jan. 7, 1953, complaining of a mass in the left side of his neck which had been noted for at least seven years. He had been told that he had a bad tonsil. He was aware of a constant sense of irritation in the left pharyngeal region. Pressure on the mass produced a sensation that caused coughing. He had been treated since 1931 for paroxysmal hypoglycemia and hypotension. For many years he had been subject to "black-out spells," particularly in the morning after arising from bed. He noted that when he raised his head he became faint and unless he lowered it he lost consciousness. Examination revealed an indefinite mass in the left upper neck presenting from beneath the angle of the mandible. The lymph nodes of the homolateral digastric triangle were enlarged, and hard, and another node approximately 2 cm. in diameter lay under the anterior border of the sternocleidomastoid muscle 3 cm. from the mastoid tip in the superior deep cervical node group. Inspection and bimanual palpation of the mass showed medial displacement of the left lateral pharyngeal wall. The tumor was seen to distort the pharyngeal air space on various roentgenograms of head and neck, which were otherwise normal. Mirror examination showed the left vocal cord to be fixed in the median position. There was puddling of secretion in the pyriform sinus, loss of gag reflex, and lag of movement of the soft palate on the left. Pressure on the tumor produced a tickling sensation in the pharynx and caused the patient to cough. Resting blood pressure was 105/65; pulse rate was 70.

Pressure over the carotid bifurcation on both left and right produced immediate asystole. The patient quickly became faint and lost consciousness if pressure was maintained. After a lapse of approximately eight beats, cardiac action returned at the rate of 40 per minute and was maintained at that rate as long as pressure over the carotid body was continued. Other findings were not significant in relation to his present complaint. Glucose tolerance test was normal.

Operation and Findings.—On Jan. 16, 1953, the tumor was exposed by postauricular and submandibular incision with division of the cervical fascia and elevation of the tail of the parotid. Lymph nodes of the digastric triangle were removed en bloc.

The relationships of the tumor to the jugular vein, the stylohyoid and posterior belly of the digastric muscle, and to the carotid complex were identical to the first case (see Fig. 2).

The neck contained numerous, dilated, fragile veins and the carotid sheath exhibited an almost hemangiomatous quality, containing many small dilated veins. There was much inflammatory fibrosis and edema in the soft tissues about the tumor and the internal carotid artery had been engulfed by this inflammatory reaction. This artery was breached during manipulation and was too degenerated to hold sutures. Proximal and distal ligation was eventually necessary, hence the superior cervical ganglion was removed.

The operation was begun with blood pressure of 105/70. During the early manipulative phase, which occupied one and one-half hours, pressure ranged from 160/100 to 180/120,

in spite of progressive blood loss without adequate replacement. Manipulation was then stopped and photographs were taken. In this period of rest the blood pressure fell to 80/60. It rose to the previous high level as soon as the operation was resumed. At this point the vagus was sectioned and the region of the carotid sinus injected with 1 per cent Novocain. Following these two procedures the pressure dropped to 80/60 and could be maintained at that level only by vigorous transfusion and administration of Neosynephrine.

Postoperative Course.—Hemiplegia did not develop although the patient exhibited mild aphasia. In spite of the preoperative paralysis of the left vocal cord, there was a distinct deterioration in the quality of the patient's voice and he has experienced persistent difficulty in swallowing.

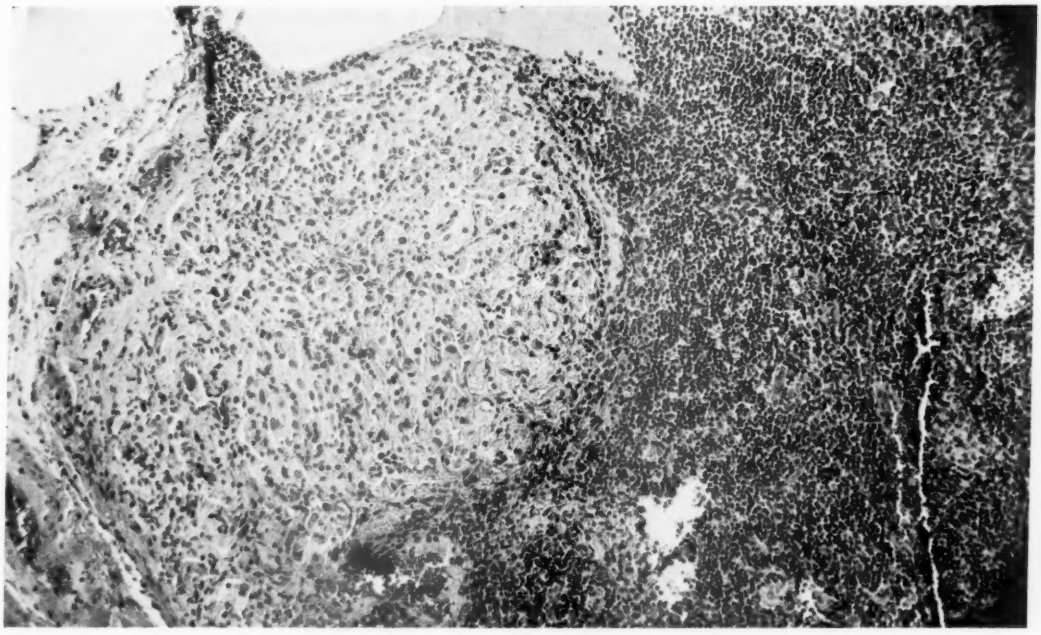

Fig. 7.—Digastric lymph node from Case 2 containing metastasis (×130; reduced ⅕).

Pathologic Findings.—

Gross: The gross surgical specimen consisted of three fragments of tumor which together formed a mass measuring 5.5 by 4.0 by 2.5 cm. A segment of vagus nerve measuring 1.8 cm. in length was attached to the most inferior of the tumor fragments. This nerve measured 0.5 cm. in diameter at the distal line of resection but 1 cm. in diameter at the inferior pole of the tumor. The tumor was encased in a fibrous capsule except at the superior border of the most superior fragment where lobules of tannish-pink, spongy tissue were exposed. On cut section this tumor was similar in all respects to the tumor described in the first case. Nine digastric lymph nodes were removed en bloc in the operative procedure. Four of these were partially replaced by tissue which was grossly identical to that in the parent tumor.

Microscopic: The microscopic structure of this lesion was similar in all respects to that described in the first case. This microscopic pattern was present in both the parent tumor and in metastases in four of the nine lymph nodes examined (Fig. 7). Chromaffin stain of the tissue by means of Schmorl's method after fixation in Orth's fluid revealed no evidence of chromaffin substance in the cytoplasm of the tumor cells. Preparation of the nerve distal to the tumor showed degeneration of many of the small, myelinated fibers. The larger fibers in the nerve did not show degeneration.

DISCUSSION

Nodular clusters of nonchromaffin paraganglionic tissue identical to that described in these tumors have been found in five locations in the body (Fig.

8). These are: (1) the region of the bifurcation of the common carotid artery, that is, the carotid body (de Castro[9]); (2) near the aortic arch, that is, the aortic bodies (Penitschka,[41] Nonidez,[39] Boyd,[6] and Bloom[4]) (there are four of these); (3) the adventitia of the dome of the jugular bulb and along the course of the ramus tympanicus of the glossopharyngeal nerve (glomus jugulare and paraganglion tympanicum; Guild,[16] and Lattes and Waltner[27]); (4) the region of the ganglion nodosum of the vagus nerve (paraganglion or glomus intravagale or juxtavagale; Muratori,[36] and White[52]); and (5) the region of the ciliary ganglion (paraganglion ciliare).

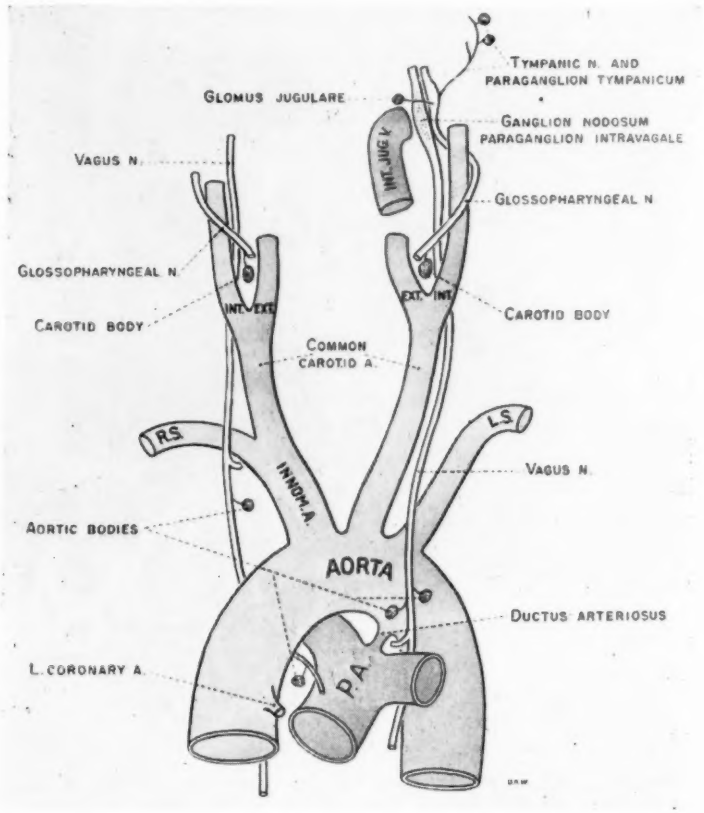

Fig. 8.—Schematic drawing illustrating sites of occurrence of nonchromaffin paraganglionic tissue. (Reproduced with the permission of Dr. LeCompte and the Armed Forces Institute of Pathology from Section IV, Fascicle 16, of the *Atlas of Tumor Pathology* published by the Armed Forces Institute of Pathology.)

The latter has been demonstrated under normal conditions only in the chimpanzee (Botar and Pribek[5]), although one case of nonchromaffin paraganglioma in the orbit has been reported in man (Fisher and Hazard[13]).

Physiologic Activity.—It has been suggested that these tissue collections represent the components of a nonchromaffin paraganglionic system (Watzka,[49] and Lattes and Waltner[27]), or a system of chemoreceptor organs (LeCompte[30-32]). The carotid and aortic bodies have been shown to be sensitive to changes in oxygen tension, carbon dioxide tension, and blood pH (Heymans and Bouckaert,[20] Schmidt and Comroe,[44] Dripps and Comroe,[11] and Hollinshead[22]). It seems likely that the collections of histologically identical tissue in the other locations listed above may have similar function.

Our 2 cases of chemodectoma of the glomus intravagale presented clinical symptoms suggesting chemoreceptor activity and vagal dysfunction: "blacking out" spells following exertion with its concomitant hyperventilation, postprandial epigastric pain, sweating, vomiting, dizziness and palpitation in Case 1; "blacking out," hypotension, and unusual carotid sinus sensitivity relieved bilaterally by operation in Case 2.

Similar symptoms of "blacking out" spells, dizziness, and nystagmus with exertion and hyperventilation were presented by a patient with chemodectoma of the glomus jugulare recently reported by Huppler and associates,[23] and these authors, likewise, suggest a possible relationship of such symptoms to chemoreceptor activity in the tumor. They made the plausible suggestion that "it is not impossible that some of the physiologic activity thought to be due to the carotid and aortic bodies alone is also due in part to the function of the normal glomus jugulare," and, we add, the glomus intravagale. Irritation of vagal fibers by pressure of the tumor may contribute to functional aberrations.

These bodies have not been shown to produce epinephrine or other internal secretion, and their cells do not contain chromaffin material thus differentiating them from the chromaffin paraganglionic system. The latter includes the adrenal medulla and the nests of paraganglionic tissue associated with the visceral sympathetic ganglia.

Embryology.—The cells forming the carotid and aortic bodies are closely associated developmentally with the third and fourth aortic arches, respectively. The relative importance of neuroectodermal and mesodermal contributions to the formation of these bodies remains a subject of controversy among embryologists. Neural elements from the glossopharyngeal, vagus, and sympathetic nerves apparently participate together with mesodermal condensations in the vicinity of the third branchial arch (Lattes[27, 28]). The controversy regarding the importance of neuroectodermal versus mesodermal contributions arises from the difficulty in following wandering embryonic cells in the region of the branchial arches (Hollinshead[21]). It is noteworthy that the carotid body, the ganglion nodosum of the vagus nerve, and the petrous ganglion of the glossopharyngeal nerve are intimately associated during early embryonic life, suggesting that the nonchromaffin paraganglionic cells of the carotid body, the glomus intravagale, and the glomus jugulare and paraganglion tympanicum may be of common origin.

Pathology and Biologic Behavior.—The characteristic features are presented in detail above. Tumors of the nonchromaffin paraganglia or chemoreceptor organs, for the most part, mimic the parent tissue very closely. In a few cases, however, pleomorphism of the chief cells and associated marked mitotic activity is observed, although the basic reticulum pattern is retained. This variation is histologic appearance has led a few authors to estimate the percentage of malignancy among carotid body tumors to be as high as 50 per cent (Harrington, Clagett, and Dockerty[17]). Clinical experience now indicates that this figure is too high and a radical approach toward surgical resection of carotid body tumors is unwarranted. Of more than 314 carotid body tumors reported in the literature (Kline, Thomas, and McNamara,[25] McNealy and Sweitzer,[34]

and Pettet, Woolner, Judd[42]), 3 cases have exhibited undisputed cervical lymph node metastases (LeCompte,[30] Sternberg,[46] and Goormaghtigh and Pattyn[15]), 2 have exhibited local invasion of the sternocleidomastoid muscle (Hendrick[18]), and 4 have exhibited visceral or bone metastases (Pendergrass and Kirsch,[40] Spotnitz,[45] Goormaghtigh and Pattyn,[15] and Turnbull[48]). These figures indicate an incidence of malignant carotid body tumors of approximately 2.5 per cent. This figure agrees very closely with the approximation of Bertrand and Sauvage[2] in 1934 when only 150 cases had been reported of which 3 or 4 were malignant.

The outlook in glomus juglare tumors is less promising. One hundred and two cases have been recognized in the literature (Huppler[23]). Of this number, 40 per cent have exhibited invasion of the skull and intracranial extension (Alexander, Beamer, and Williams,[1] Dockerty, Love, and Patton,[10] and Huppler[23]), 3 cases have shown cervical lymph node metastases (Winship, Kopp, and Jenkins,[53] Lahey and Warren,[26] and Poppen and Riemenschneider[43]), and 1 patient developed liver metastasis (Lattes and Waltner[27]).

Seven cases of nonchromaffin paraganglioma of the ganglion nodosum of the vagus nerve have been reported at this writing (Lattes,[28] Birell,[3] Burman,[7] Huppler and associates,[23] and King[24]). One of Lattes' cases was previously reported by Stout,[47] in 1935, under the diagnosis of "pigmented malignant paraganglioma of the ganglion nodosum in the vagus nerve." This patient was alive without evidence of recurrence at the time of publication of Lattes' article, seventeen years after surgical excision. One of Lattes' patients died as a result of recurrence of ganglion nodosum tumor following attempted surgical excision. Invasion of the base of the skull was demonstrated at autopsy. An independent histologically similar tumor of the carotid body on the opposite side was found at autopsy. Lattes' third case had an inoperable tumor of the ganglion nodosum which was biopsied during life. Death occurred as the result of bulbar poliomyelitis seven months after diagnosis of the ganglion nodosum tumor. Independent tumors of one carotid and one aortic arch body were incidental findings at autopsy. The tumor in King's case was successfully removed but required sacrifice of the right ninth through the twelfth cranial nerves in the process. Our second case exhibited metastases in four of nine cervical lymph nodes removed.

Lattes[28] reported two instances of aortic body tumors in man. One of these occurred in the third case of ganglion nodosum tumor which he reported and which is described above. The other patient had a very large tumor arising in the mediastinum which bulged into the right supraclavicular fossa. Total resection of the tumor was deemed impossible and partial resection of the cervical extension was carried out. The patient was alive with residual tumor three years and eleven months after this operation.[29]

Duncan and McDonald[12] reported 2 cases of chemodectoma of the mediastinum (presumably arising in aortic bodies). McDonald, Aufderheide, and Fuller[33] reported the fifth case of chemodectoma of the mediastinum.

In 1952, Fisher and Hazard[13] recognized the first nonchromaffin paraganglioma of the orbit in man. As yet the counterpart of the paraganglion ciliare of the chimpanzee has not been demonstrated in man. The occurrence

of such a tumor in this location, however, suggests that a paraganglion ciliare may be an inconstant structure present in the orbits of a few individuals. This tumor presented no histologic evidence of malignant properties.

SUMMARY AND CONCLUSIONS

1. The literature indicates that the majority of chemodectomas or nonchromaffin paragangliomas are benign tumors.

2. A small percentage which exhibit a less regular histologic pattern invade locally and may metastasize to lymph nodes, viscera, or bone.

3. The glomus intravagale tumors, as a group, are more aggressive than carotid body tumors. Three of the 9 reported cases have exhibited malignant characteristics showing, respectively, local bony invasion, widespread bone metastases, and lymph node metastases.

4. The combination of a mass in the neck and symptoms indicating altered chemoreceptor and vagal activity should suggest the clinical diagnosis of chemodectoma although the exact site of origin of the lesion may not be apparent until after surgical exposure.

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THE INFLUENCE OF TRANSURETHRAL RESECTION ON SURVIVAL IN ADVANCED PROSTATIC CARCINOMA

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INTRODUCTION

THE most satisfactory method of relieving bladder neck obstruction due to carcinoma of the prostate gland has been transurethral resection, since this lesion does not lend itself to open enucleative procedures whether suprapubic, perineal, or retropubic, because of the diffuse involvement by malignant tissue which infiltrates the bladder neck and allows no easily definable anatomic plane of cleavage essential for satisfactory enucleation.

Nevertheless, a critical evaluation might suggest to the urological surgeon that this operative procedure would appear to contravene some of the most fundamental principles governing good cancer surgery. Here is an operation which requires bold cutting into malignant tissue, opening blood vessels and lymphatics and then forcing irrigating fluid under some pressure into the prostatic urethra as if better to disseminate cancer cells into the circulation. At the same time, some inevitable manipulation of the resectoscope appears to massage the neoplasm further, this with the prostatic vessels open.

It has been adequately shown that a substantial amount of irrigating fluid may be introduced directly into the circulation through the open prostatic veins during the performance of transurethral resection.[1-3, 7, 9, 10]

From these observations it would seem not unlikely that widespread dissemination of cancer cells may occur during transurethral resection, and yet in clinical practice one observes that most patients do not go rapidly downhill from widespread carcinomatosis following transurethral resection, although an occasional patient does do so.

Although this operation is not designed to cure prostatic cancer but simply to re-establish normal micturition and prevent hydronephrosis due to bladder neck obstruction, a surprisingly high percentage of patients, 43[11] to 46 per cent,[5] with prostatic carcinoma too extensive for hope of cure by radical prostatectomy,[14] but not showing bone metastases, will survive five years or more if treated by bilateral orchiectomy and stilbestrol and if the bladder neck obstruction is relieved by transurethral resection.

It, therefore, seemed reasonable to study a series of patients with prostatic carcinoma and to see whether the overwhelming preponderance of transurethral resections were carried out on the group that failed to survive five

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years or whether the distribution was about equal in the two groups. If it could be shown that very few transurethral resections were performed in the five-year survivors and many in the nonsurvivors, it would be reasonable to conclude either that transurethral resection has a deleterious influence on five-year survival or that the group requiring transurethral resection had more severe bladder neck obstruction due to locally more extensive prostatic carcinoma.

INVESTIGATION

The records of a consecutive group of patients with late carcinoma, too advanced for cure by radical prostatectomy, were studied. All patients had unequivocal evidence of prostatic carcinoma and all were treated by bilateral orchiectomy and stilbestrol,[8] usually 5 mg. daily. The group was clinically controlled in the sense that all of these patients, though harboring locally extensive carcinoma, were shown to satisfy three clinical criteria as follows: (1) Normal serum acid phosphatase—less than 3.1 Gutman Units,[6] (2) No demonstrable bone metastases, and (3) No evidence of hydronephrosis by pyelography.

All patients were followed five years or longer.

Forty-four patients satisfied these criteria. Seven of these patients died of unassociated disease before the fifth year. Of the remaining 37 patients, 22 or 59.4 per cent survived five years or longer. Fifteen patients or 40.6 per cent of the group died of carcinoma of the prostate before the fifth year. The incidence of transurethral resection was studied in these two groups.

Among the 22 five-year survivors, transurethral resection was performed 27 times.

Among the 15 nonsurvivors, transurethral resection was performed 15 times.

In the entire series of 37 patients, 26 patients had one or more transurethral resections and 11 patients had no transurethral resection.

Among the 11 patients without transurethral resection, there were 5 five-year survivors, a percentage of 45.4.

Among the 26 patients with one or more transurethral resections, there were 17 five-year survivors, a percentage of 65.4.

Three of the five-year survivors had 3 transurethral resections each, and 4 had 2 transurethral resections each.

Since it may seem that this series is too small to allow any significant conclusions, a study of the incidence of transurethral resection in a consecutive group of patients with late prostatic carcinoma treated by orchiectomy and stilbestrol plus transurethral resection when indicated for the relief of bladder neck obstruction was carried out. All patients had advanced prostatic carcinoma too extensive for radical prostatectomy but were free of demonstrable bone metastases when first seen or treated. The records of 48 consecutive five-year survivors and 48 consecutive nonsurvivors (all of whom had died of prostatic carcinoma before the fifth year) were reviewed.

Among the 48 five-year survivors, 37 patients had had transurethral resection.

Among the 48 nonsurvivors, 33 patients had had transurethral resection.

In the entire group of 96 patients, 70 patients had one or more transurethral resections and 26 patients had no transurethral resection.

Among the 26 patients who had no transurethral resection, there were 11 five-year survivors, a percentage of 42. Among the 70 patients who had transurethral resection there were 37 five-year survivors, a percentage of 53.

DISCUSSION

It is of interest that Eisendrath and Rolnick,[4] in the 1938 edition of their textbook *Urology*, stated that transurethral resection "hastens the spread of carcinoma and undoubtedly aggravates the other symptoms due to extension or metastases. While resection establishes a groove, it hastens the spread of the growth by cutting through the capsule and thus its value can also be seriously questioned." It is to be remembered that this was written in the era before antiandrogenic treatment of prostatic malignancy.

On the other hand, Nesbit and Plumb[12] were able to show that patients who had transurethral resection without antiandrogenic treatment had a longer survival than patients with no treatment whatever, and these authors felt that the "resection operation probably did not cause acceleration of the malignant growth or extension of metastases." Their observations, published in 1946, were based on a study of survival in 605 patients with prostatic carcinoma treated before the endocrine era.

If transurethral resection produces widespread dissemination of cancer cells, one would expect a higher incidence of death from prostatic carcinoma before the fifth year in the patients who had transurethral resection than in those who did not require it. It is reassuring, however, that such was found *not* to be the case.

The differences noted in the figures representing five-year survivorship in the first and second series are easily explained by the fact that some of the patients in the large series, although free of bone metastases, did have hydronephrosis or elevation in the level of serum acid phosphatase, both of which have been shown to have a deleterious influence on five-year survivorship in patients with locally extensive prostatic carcinoma treated by orchiectomy and estrogens.[5]

The possibility remains that widespread dissemination of cancer cells may occur but that these cancer cells fail to take root in the new environment and do not continue to multiply to develop into metastatic growths because of "infertile soil."[13] Perhaps hormonal imbalance produced by orchiectomy and stilbestrol therapy may be one of the factors that help to render the "soil infertile" for the growth of these disseminated cancer cells.

CONCLUSIONS

Although transurethral resection of the obstructing malignant prostate presents some theoretical objections from the standpoint of the general surgical principles governing the prevention of operative spread of cancer cells, it cannot be shown that this operation has an adverse influence on five-year survival in a clinically controlled series of patients with advanced prostatic carcinoma, under anti-androgenic control with orchiectomy and estrogens.

If widespread dissemination of cancer cells occurs, it must be assumed that the cells fall on relatively infertile soil and fail to develop rapidly into clinically demonstrable metastases, possibly, in part, because of the modification of the internal environment produced by orchiectomy and estrogen therapy.

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THE DEVELOPMENT OF ANASTOMOTIC STRICTURES IN DEFUNCTIONALIZED BOWEL

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THE incidence of anastomotic strictures in defunctionalized bowel is probably not great, but the development of such strictures more frequently following closed anastomoses has been commented upon by Welch, Allen, and Donaldson.[6] Our clinical experience consists of 2 patients in whom strictures developed at the site of left colon anastomoses performed by the closed method in defunctionalized bowel. In both cases the surgeon was assured, at the time of creation of the anastomosis, that the stoma was patent on digital examination. In view of this clinical experience, the literature was reviewed for experimental or clinical evidence to show that there is or is not a difference in the healing of open and closed anastomoses in defunctionalized bowel. As no prior work on this particular problem was uncovered, the question was brought to the experimental laboratory for possible solution.

METHODS AND MATERIALS

Mongrel dogs, weighing between 8 and 18 Kg., were used for these experiments. Each dog was subjected to two operative procedures, and several weeks after the second operation was sacrificed for removal of the colon. All operative procedures were performed aseptically under intravenous Nembutal anesthesia, through an upper abdominal midline incision. Penicillin, 300,000 u., and di-hydrostreptomycin, 1 Gm., were placed in the peritoneal cavity before closure of the abdomen; these drugs were also administered for three days postoperatively. The dogs were starved for twelve or more hours preoperatively, and were allowed food and fluids ad libitum after each operation. The first-stage operation was essentially the creation of the preparation; it resulted in isolating a long segment of defunctionalized large intestine. In the first 8 dogs, the first-stage procedure was done by dividing the terminal ileum and the descending colon, performing an ileoproctostomy, turning in the two remaining ends of bowel, and bringing out the appendix through the abdominal wall as an appendicostomy (Fig. 1, *A*). This preparation worked fairly well, but because of small amounts of inspissated material encountered in the colon of several animals at the second-stage operation, the preparation was modified to that depicted in Fig. 1, *B*. In this second preparation, the ileum and sigmoid colon were divided and an ileoproctostomy performed. After inverting the distal ileum and suturing it to the lateral parietal peritoneum to prevent intussusception, the proximal descending colon was brought out through a stab wound as a colostomy. Better defunctionalizing of the colon was produced by this operation, probably because the colostomy was at the aboral end of the isolated loop.

In order to compare the behavior of open and closed anastomoses in defunctionalized bowel, identical operations were performed in two groups of animals, the only difference being in the method of suturing the anastomoses. In every animal, both anastomoses (the ileoproctostomy in the first operation and the critical anastomosis at the second

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operation) were done by the same technique. In this way, the behavior of the functional ileoproctostomy served as a control for the critical anastomosis performed in the defunctionalized bowel in the same animal.

Two weeks after the first operation, the animals were reoperated upon, and a short segment of transverse colon was resected. The anastomosis of these two cut ends of transverse colon constituted the critical anastomosis. This was done, as mentioned above, by the open or closed method and in all instances the bowel was divided obliquely and anastomosed in that fashion. In order to avoid kinking at the anastomotic site due to this obliquity, the mesenteries were reversed, as described by Dennis[1] (Fig. 1, *C*). The

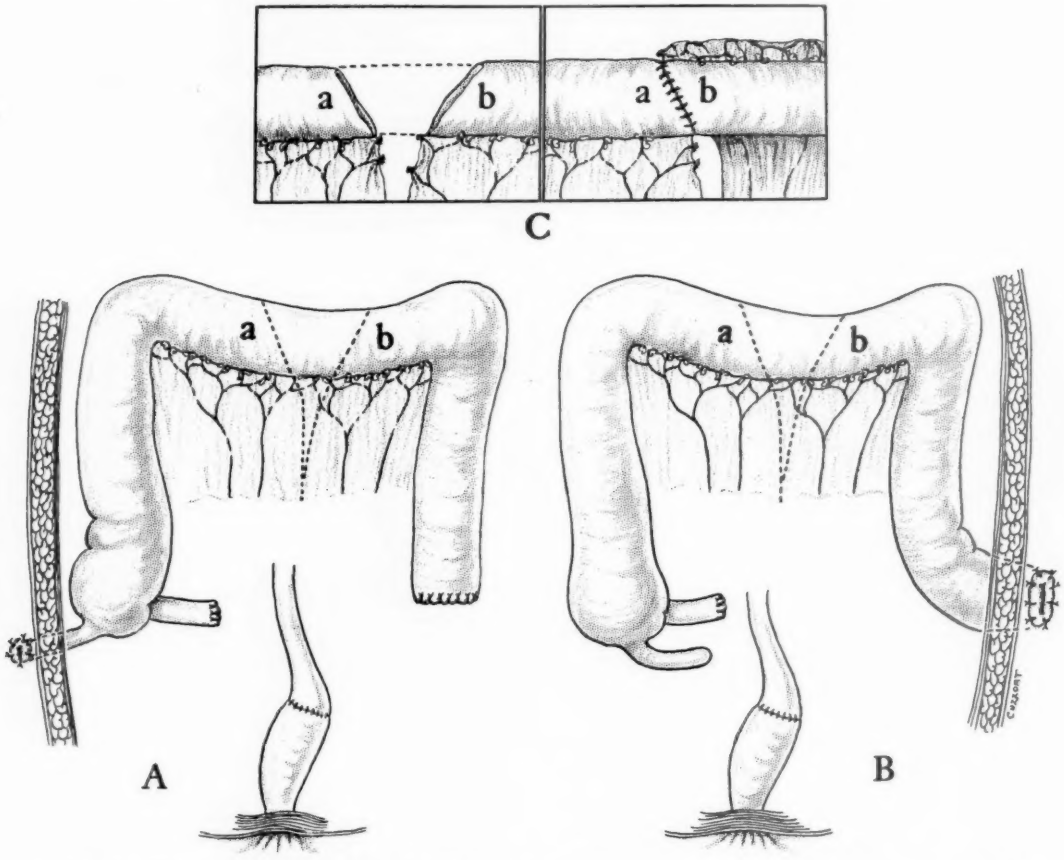

Fig. 1.—*A*, Original method for isolating a defunctionalized segment of colon. *B*, Revised method for isolating a defunctionalized segment of colon. *C*, Technique of oblique resection, reversal of mesenteries, and resulting unkinked anastomosis.

closed anastomoses were performed with Dennis clamps, using a single row of interrupted 4-0 bblack silk Lembert sutures. The open anastomoses were made with an inner row of continuous, locked 3-0 chromic catgut and an outer row of 4-0 silk Lembert sutures. To confirm patency in the closed anastomoses, a small colotomy was made in the proximal limb and a Carmalt hemostatic forceps inserted past the anastomosis for several inches into the distal loop. This colotomy was then closed with several Lembert sutures.

Three to four weeks after the second operation, the animals were sacrificed (using intravenous Nembutal), and the entire intestinal tract was removed for study. The critical anastomosis in the transverse colon was inspected, photographed, and preserved in formalin. Any decrease in the lumen was noted and the diameter measured. The functioning ileoproctostomy, in addition, was examined in each animal. Sections of many of the fixed specimens were mounted in paraffin, stained, and subjected to microsocopic study.

RESULTS

A total of 33 dogs survived both operations and were studied at autopsy. In 21 of these animals, the anastomoses were performed by the closed technique, and in the remaining 12 by the open method. The first 8 animals were operated upon according to the method shown in Fig. 1, *A*. The incidence of complete or partial septum formation at the critical anastomosis in these

Fig. 2.

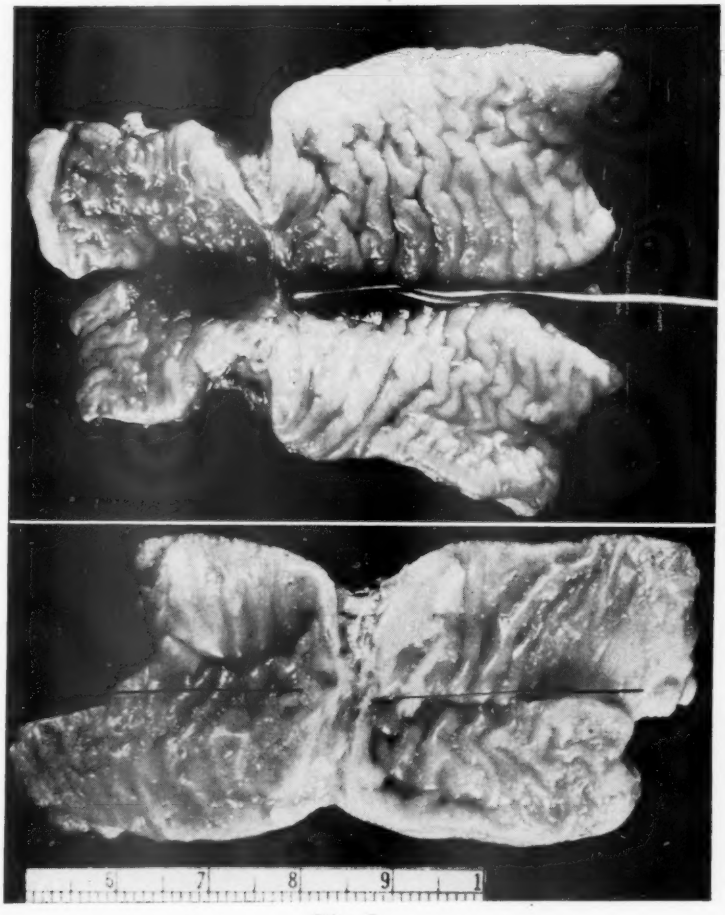

Fig. 3.

Fig. 2.—(Dog No. 648.) Appearance of closed anastomosis in defunctionalized bowel after four weeks.

Fig. 3.—(Dog No. 583.) Closed defunctionalized anastomosis with septum formation. Septum has been divided to demonstrate wedge-shaped base.

TABLE I. CLOSED ANASTOMOSIS (OPERATION DESCRIBED IN FIG. 1, *A*)

DOG NO.	PATENCY OF ANASTOMOSIS
321	Completely patent
342	Complete septum
487	Very large diaphragm; luminal diameter 3 mm.
509	Definite stenosis; luminal diameter 1 cm.
583	Definite stenosis; luminal diameter 1 cm.
597	Complete occlusion*
627	Completely patent
648	Very large diaphragm; luminal diameter 2 mm.

*Small abscess about 2 cm. from anastomosis. Moderate reaction and adhesions in this area.

animals is shown in Table I. Of the 8 anastomses studied, only 2 were completely patent, one had a slight spur formation, and the others had large spurs or complete, water-tight diaphragms (Figs. 2 and 3).

Fig. 4.

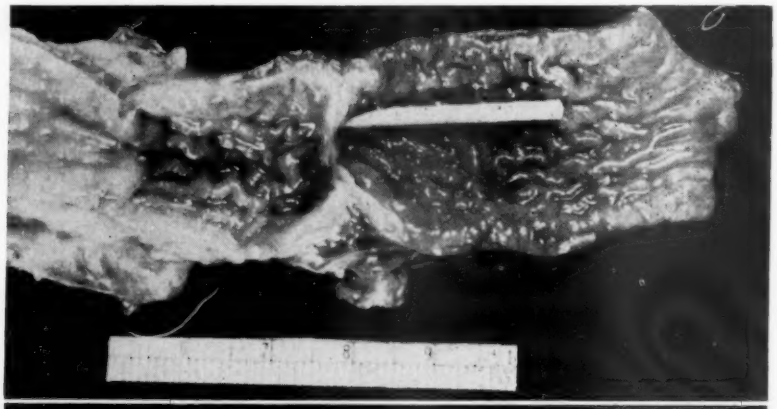

Fig. 5.

Fig. 6.

Fig. 4.—(Dog No. 176.) Complete diaphragm in a closed defunctionalized anastomosis. Septum has been divided to illustrate wedge-shaped base.

Fig. 5.—(Dog No. 799.) Bowel has been opened showing complete diaphragm. The latter has been divided. Note markedly dilated, thin-walled, proximal segment.

Fig. 6.—(Dog No. 852.) Note intussusception of ileum proximal to diaphragm. Clamp illustrates extent of this septum, which left a lumen 2 mm. in diameter.

Fig. 7.

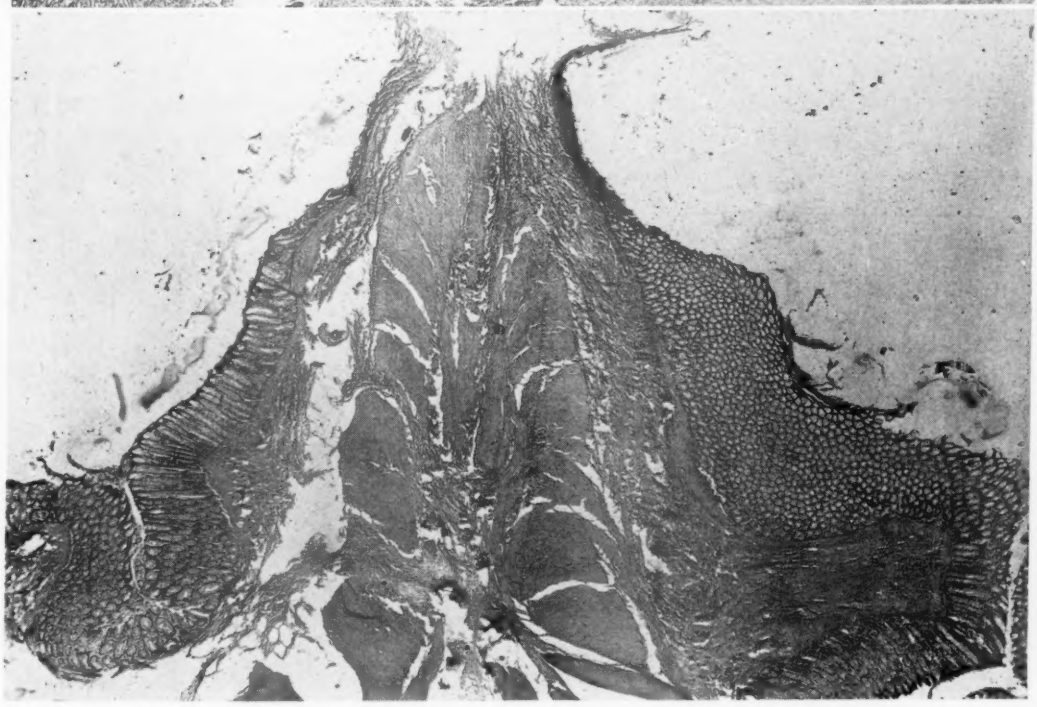

Fig. 8.

Fig. 7.—(Dog No. 799.) Photomicrograph of septum showing absence of the epithelium at the apex, and bands of muscularis (Hematoxylin and eosin; ×16; reduced ¼).

Fig. 8.—(Dog No. 396.) Photomicrograph of septum. Here the epithelium nearly completely covers the apex (Hematoxylin and eosin; ×16; reduced ¼).

Thirteen animals were operated upon according to the operation shown in Fig. 1, *B*, with all anastomoses having been performed by the closed method. The results in this group are shown in Table II. Five of the critical, defunctionalized anastomoses were satisfactorily patent, and one was moderately occluded, with a remaining intraluminal diameter of only one centimeter. The other seven were markedly constricted by spur formation or completely impermeable (Figs. 4, 5, and 6).

TABLE II. CLOSED ANASTOMOSIS (OPERATION DESCRIBED IN FIG. 1, *B*)

DOG NO.	PATENCY OF ANASTOMOSIS
176	Complete diaphragm
372	Complete diaphragm
396	Partial septum; luminal diameter 4 mm.
424	Complete diaphragm
657	Partial septum; luminal diameter 6 mm.
723	Partial septum; luminal diameter 1 cm.
799	Complete diaphragm*
847	Completely patent
852	Nearly complete diaphragm; luminal diameter 2 mm.†
853	Minimal septum; lumen adequate
863	Completely patent‡
3	Completely patent
30	Completely patent

*Marked distention of colon proximal to diaphragm.
†Inverted ileum had intussuscepted up to diaphragm.
‡Inverted ileum had intussuscepted through the anastomosis.

Twelve animals were studied in which the anastomoses were performed by the open technique. All of these operations were done according to the arrangement illustrated in Fig. 1, *B*. In none of these animals was there any evidence of septum formation or limited lumen at the critical anastomosis.

The histologic picture of the functional anastomoses in both groups, and of the open anastomoses performed in defunctionalized bowel, was similar. In all of these, the anastomotic site was fully epithelized. The muscularis mucosae was absent for several microscopic fields from the actual site of anastomosis, and proliferating submucosa appeared to fill the gap between the muscularis and the muscularis mucosae of the two cut ends of bowel. The serosa was intact. Without exception, there was a satisfactory lumen in these specimens; the mucosa had grown completely over the anastomotic site. Any spur caused by the operative procedure was minimal or nonexistent.

The histologic pattern of the anastomoses performed by the closed method in the defunctionalized bowel, and in which septa had developed, was different. The epithelium had grown up along the base and sides of the wedge-shaped septum, diminishing in thickness as it approached the apex; epithelium was absent from the very apex (Figs. 7, 8, and 9). Proliferated submucosa and inverted muscularis constituted the body of the septum. The serosa was intact.

Isolated observations made on three-day-old closed anastomoses revealed a broad necrotic bed at the junctional site, measuring 3 to 4 mm. in width. This represented the portion of bowel wall (previously crushed by the anastomotic clamps) which had been inverted into the lumen. Since the blades of the clamps were in apposition at the time the anastomosis was performed, it

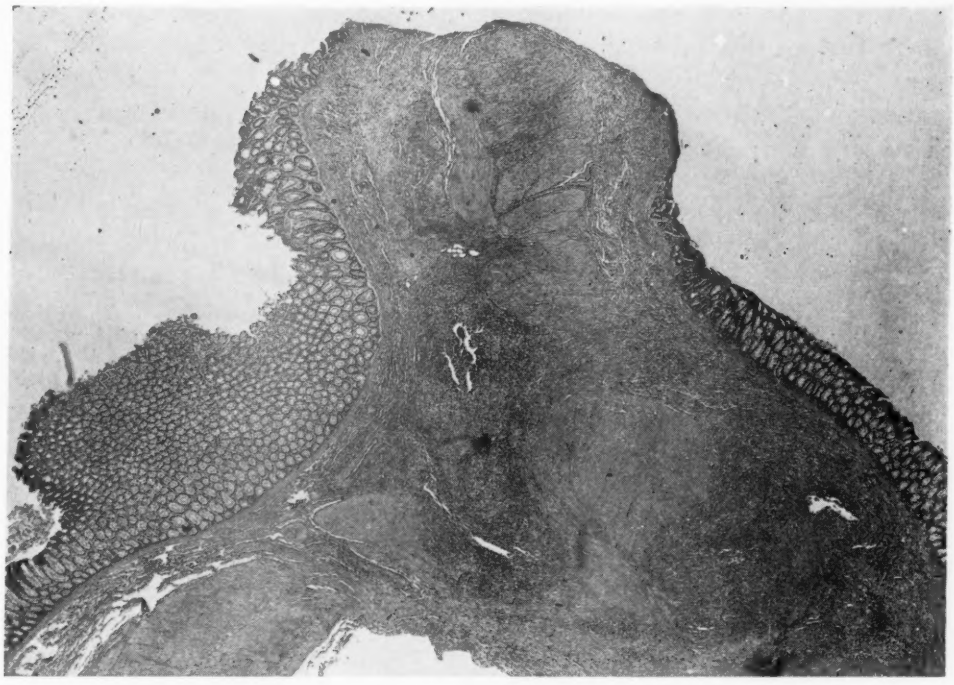

Fig. 9.—(Dog No. 424.) Photomicrograph of wedge-shaped septum illustrating absence of epithelium at apex, islands of muscularis and proliferated submucosa (Hematoxylin and eosin; ×16; reduced ¼).

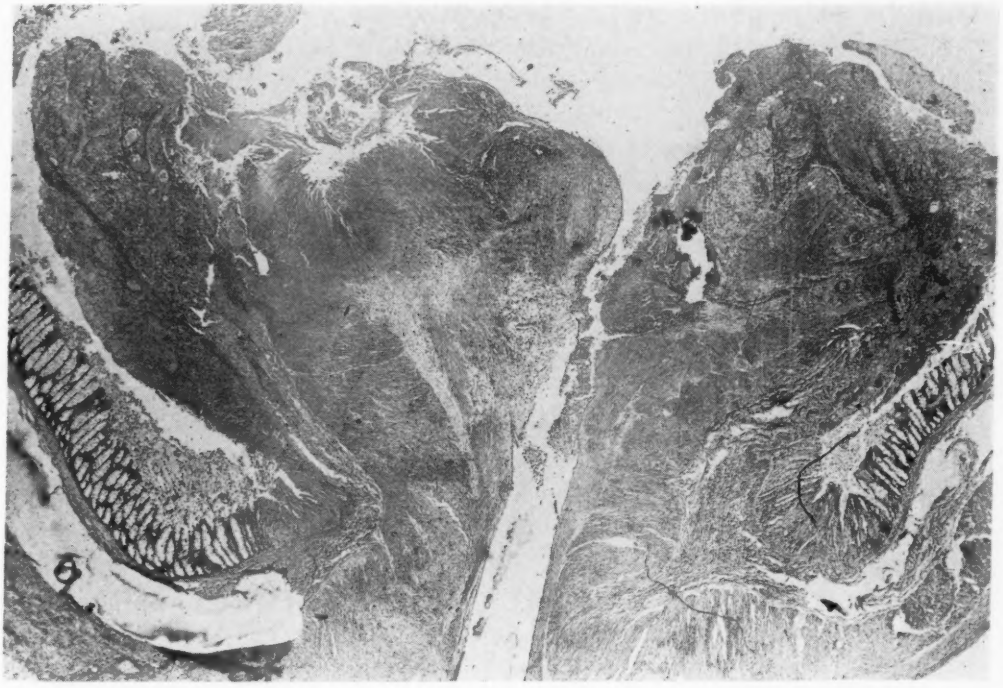

Fig. 10.—(Dog No. 990.) Photomicrograph of a closed anastomosis three days after performance. There is a broad, inverted segment of necrotic bowel involving all layers (Hematoxylin and eosin; ×16; reduced ¼).

is apparent that there was a significant increase in the width of this crushed segment during this initial period of healing (Fig. 10). Microscopically, this appears to be the result of a marked inflammatory reaction. At defunctionalized anastomoses, this broad base of inflammatory tissue does not slough away, but persists as a wide bed of fairly active fibroplasia.

DISCUSSION

The development of partial septa and diaphragms with such frequency at the site of defunctionalized closed anastomoses seems significant. The animals in both groups were of similar size and were operated upon by the same two surgeons. Inspection of the critical anastomoses took place following equal periods of time after their creation in each series. In all animals (open and closed groups) efforts were directed toward creating the largest possible lumen at the defunctionalized anastomotic site. The obliquity of the anastomotic line was an attempt to accomplish this. Meticulous care was taken to invert as little tissue as possible in all anastomoses. In addition to providing the largest possible lumen at the stoma, the obliquity resulted in an elliptical suture line; theoretically this permits less contact of granulating surfaces than does a circular anastomosis. It seemed to us that anastomoses with increased patency could be ascribed to this obliquity because partial spurs were occasionally found, and only at those sites where opposing granulating beds were in contact. If the granulating surfaces were circular, it seems likely that there would be contact of much more of the circumference of this circular bed and, as a result, a more complete septum.

The reasons for the development of these septa are suggested by this study. The functional closed anastomoses remained patent in all instances, as did the defunctionalized open anastomoses. Why did the defunctionalized closed anastomoses often behave differently? To us the factors are several: the obturative action of the intestinal content, the inversion of crushed bowel and mucosal approximation by suture.

The inverted spur of crushed intestine becomes very wide and inflamed during the first few days after performance of a closed anastomosis (Fig. 10), but in functional anastomoses it quite rapidly shrinks and is completely covered by epithelium within fourteen to sixteen days. In defunctionalized anastomoses, however, it often remains as a large cuff containing proliferating fibroblastic elements, and does not become covered with mucosa. This crushed portion of bowel does not, in our experience, slough away at the defuctionalized anastomosis, as attested by the presence of viable muscle and submucosal elements in the body of the septum.

The difference in behavior of functional and defunctionalized closed anastomoses can certainly not be attributed to inversion of crushed spur, and seems to us to be partly explained by the presence of the fecal stream in functional bowel. This material nearly continually separates the portions of the granulating bed at the anastomosis, preventing agglutination and subsequent fibroblastic union. Agglutination appears to us to be the important factor, since many of the incomplete septa had lumina which were eccentric in position,

and appear to be more readily explained by agglutination of parts of the granulating bed rather than by cicatrization, which should be a circumferential process.

The freedom from septa or strictures in the open, defunctionalized anastomoses seems most attributable to accurate mucosal suturing. This prevented the possible contact of opposing segments of a circumferential granulating bed such as is present in the closed, defunctionalized anastomoses.

Our limited clinical experience, coupled with the experience of Welch, Allen, and Donaldson,[6] and the findings of this experimental study, suggest that it is probably unwise to perform an anastomosis of the closed type (using crushing clamps) in a segment of colon which has previously been defunctionalized and remains so following the procedure. This caution possibly also obtains in those circumstances where primary closed anastomoses are made and the bowel defunctionalized by a proximal colostomy. However, because of the many distinct advantages of the closed technique, which have been described and emphasized by others,[2-5] we continue to employ it in preference to the open method in small and large bowel anastomoses that remain functional.

SUMMARY

1. Limited lumina resulted in 12 of 21 anastomoses performed by the closed technique in previously defunctionalized colons in dogs. Six of these were complete, water-tight septa.

2. In 12 anastomoses performed by the open method in previously defunctionalized colons in dogs, no limitation in the lumen resulted.

3. No limitation in the lumen resulted at any of the functional anastomoses performed by either method in these dogs.

4. The possible reasons for the development of these spurs and septa are discussed.

5. Further experiments are in progress to elucidate which factor or factors are most operative in the development of these strictures.

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MANAGEMENT OF HEMATOGENOUS PYOGENIC OSTEOMYELITIS

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SUCCESSES with modern chemotherapy have pushed the basic concepts of acute, subacute, and chronic hematogenous pyogenic osteomyelitis into limbo and off the pages of medical journals. One wonders what younger surgeons think when they are confronted with variants of this protean disease, that is, cases which go on to local infection and/or sequestrum formation. Surely, then, there emerges the need for traditional knowledge of the natural clinical life history of this disease. I shall develop this theme and superimpose principles of control along the same lines.

PATHOGENESIS

Fig. 1 delineates the pathogenetic factors which govern the outcome in acute hematogenous pyogenic osteomyelitis. Thus hypothesized, certain clinical probabilities may be derived because of the limitations which this picture imposes upon the clinical life history of the disease. First, the disease is activated by a bacteremia and a thromboembolic process in or near a bone or bones. Second, this relationship between the superimposed general and local infection is fundamental for all kinds and variants of the disease. Third, the outcome will depend upon the intensity of the bacterial infection, the defensive mechanisms of the body—humeral and cellular—and the extent and quality of the local lesion. Clearly, then, the disease is a self-limited one; and, moreover, the outcome is unpredictable at onset or in the early stages. Experience has taught that three patterns of the disease may be expected: abortive, arrestive, and suppurative forms.

In the abortive types the disease has not gone beyond the stage of bacterial seeding and both the general and local infections have been controlled—spontaneously or by treatment. The patient gets well without residual bony changes which are discernible on x-ray films. This happens only in the first or second weeks of the disease. The clinical episode is then closed for all practical purposes; but the patient ought to be checked later on for possible so-called "silent foci" in bone (a Brodie-like lesion). At the other extreme, death rarely ensues because of an uncontrolled bacteremia and toxemia in the first week of the disease (frequently observed before the days of modern chemotherapy).

The next stage in the mechanistic concept of the disease implies that bacterial fixation has occurred in the bone. An arrestive and/or nonsuppurative lesion still means that the local situation is under control, as well as the general infection. Cellular defensive action has prevented frank suppuration and the

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resultant bony lesion is a bland one—an infaret if it is notable on x-ray as a variant of sequestrum formation (attached or isolated from the surrounding bed) (Fig. 3).

In arrestive forms, aside from possible future flares, a complete restitution of bone may be expected so long as mechanical protection is provided (brace or cast) until this occurs. Arrestive forms are an important link in the evolution of the disease from the standpoint of both diagnosis and treatment. The first involves differentiation from tumor (if the lesion is seen some weeks or months after onset); the second demands surgical restraint so long as the lesion has become clearly localized and identified as a nonsuppurative type. Arrestive forms of the disease may be considered to be mid points between abortive and suppurative lesions. (Figs. 4, 5, and 6.)

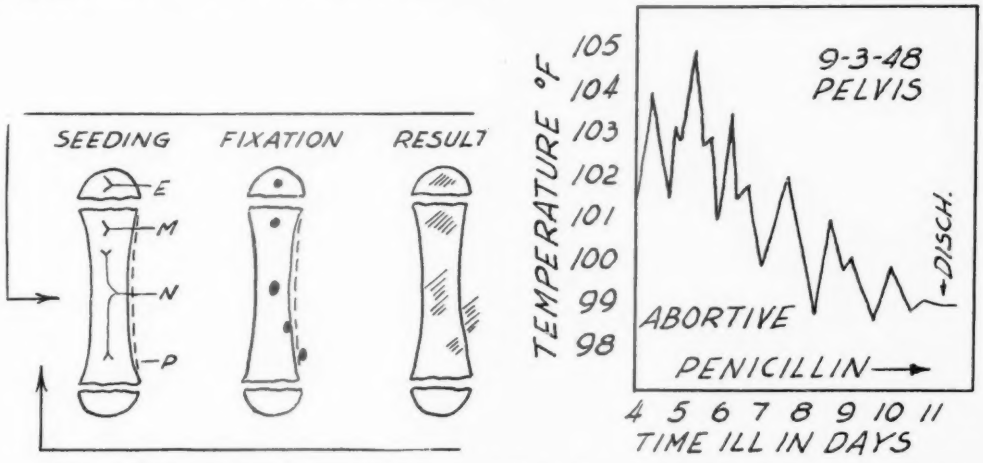


Fig. 1.—Bacteremia. Schematic representation of pathogenesis of acute hematogenous pyogenic osteomyelitis: local lesion develops on basis of a retrograde thromboembolic process; *N* is the nutrient vessel, *M* is the metaphyseal and *P* the periosteal arterial supply. The classic localization is metaphyseal; it may be subperiosteal, paraosteal, in the shaft, cortical, and even rarely in the epiphysis. The trigger or bacterial portal of entry is usually unknown but often conjectured to be a topical infection. Trauma and lowered bodily resistance (of whatever cause) are thought to be predisposing factors.

Fig. 2.—Chart of boy, aged 13 years, with impending osteomyelitis of the pelvis, aborted with penicillin therapy alone and plaster spica for one month; recovery was complete and permanent.

Suppuration represents the successful result of infection over the local cellular defensive reaction to it. Suppuration may or may not be associated with concurrent exfoliation of bone. The latter cannot be predicted in the first stages of infectious localization in bone. This predicates a conservative attitude (Figs. 7, 8, and 9) or surgical policy at that time (simple drainage of the paraosteal abscess only). The critical point in this regard is the actual exfoliation of the sequestrum from the host bone bed. When this occurs in the presence of suppuration (initial stages or later flares), surgical removal of the sequestrum (Fig. 10) is clearly indicated. As a rule, local suppuration indicates that the general infection is apparently under control and that the disease will now continue as an independent condition. The mortality, under such circumstances, is usually nil in the uncomplicated cases. Flares always recall the basic corelationships between the general and local infections.

CLINICAL LESSONS OF THE PAST

Prior to 1936 the vast majority of surgeons advocated and practiced immediate surgical interference in all cases of acute hematogenous osteomyelitis which were admitted to the hospital in the early stages of the disease. An

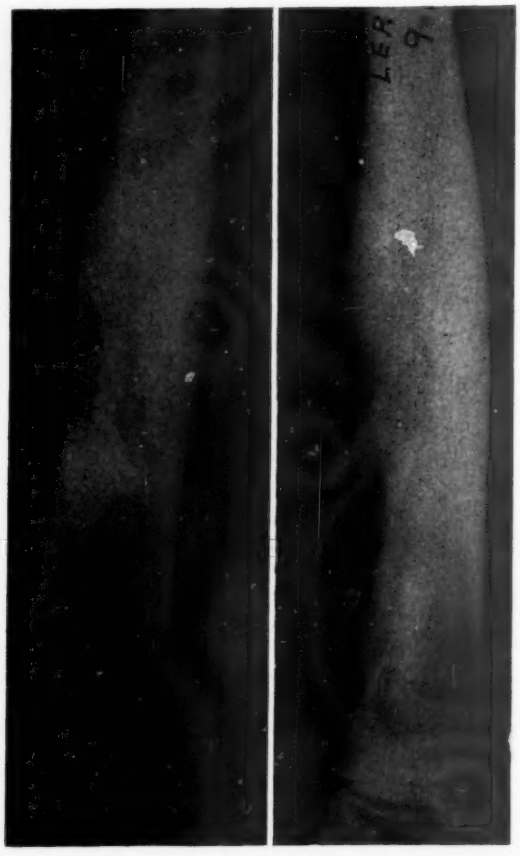


Fig. 3.—Roentgenogram of femur in boy, aged 9 years, eleven months, after acute onset and spontaneous regression of general and local infection. Now an acute flare-up required surgical removal of the sequestrum (which healed after primary closure of the operative wound). This case represents what may be termed a spurious arrest of the disease. There was some lengthening of the femur from stimulated growth by irritation of the sequestrum.

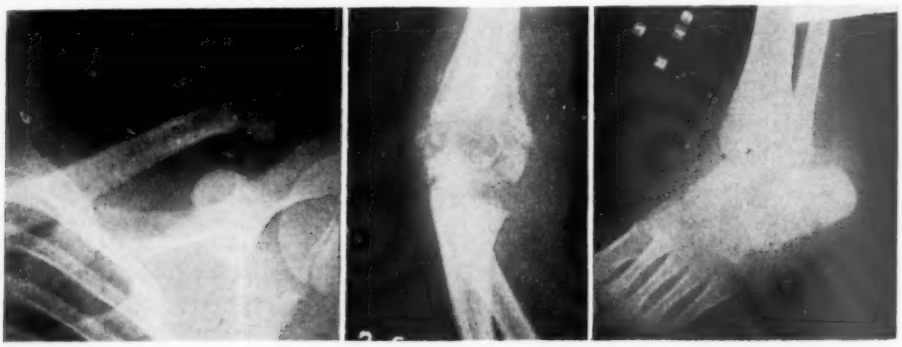


Fig. 4.—Roentgenograms of clavicle, elbow, and os calcis in boy aged 7 years; all lesions evolved on basis of simple fractures but only the os calcis went on to suppuration (which required surgical interference).

TABLE I.—MORTALITY WITH REFERENCE TO INTERVAL BETWEEN ONSET OF ILLNESS AND THE TIME OF OPERATION*

DURATION OF ILLNESS (WEEKS)	CONSERVATIVE OPERATION			RADICAL OPERATION			TOTAL RESULTS		
	CASES	DIED	PER CENT	CASES	DIED	PER CENT	CASES	DIED	PER CENT
First	6	2	33.3	14	5	35.7	20	7	35
Second	13	1	7.7	11	2	18.2	24	3	12.5
Third-Fourth	14	1	7.1	14	2	14.3	28	3	10.7
Total	33	4	12.1	39	9	23.1	72	13	18.1

*Postoperative mortality in series of 72 cases of acute hematogenous pyogenic osteomyelitis treated before the advent of chemotherapy. The majority of the operations were radical (bone was also attacked at the primary operation). The conservative operation indicates that the bone was not attacked at the primary operation. It is to be noted that all operations performed in the first week of the disease were attended by a high mortality—whether conservative or radical. The operative mortality dropped markedly after the second week of the disease; but less so in radical operations.

analysis of the temperature charts of 72 cases studied by the author at that time (Fig. 11) (which were treated by various members of the medical and surgical staffs of the Missouri Methodist and St. Joseph Hospitals) would indicate that the first week of the disease hardly constituted the best period in which to operate upon these sick patients; however, this was the generally accepted practice at the time. Time and progress changed this kind of surgical policy to one of conservatism or restraint until frank suppuration had occurred. The latter attitude prevails today, and was bolstered (even years ago) by a study of the operative results in the 72 cases mentioned above (Table I).

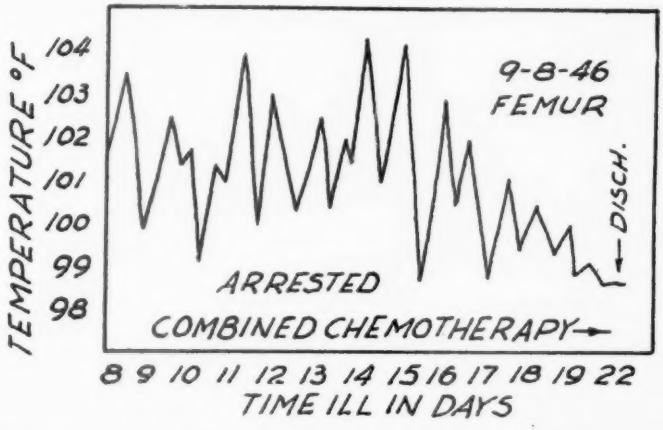
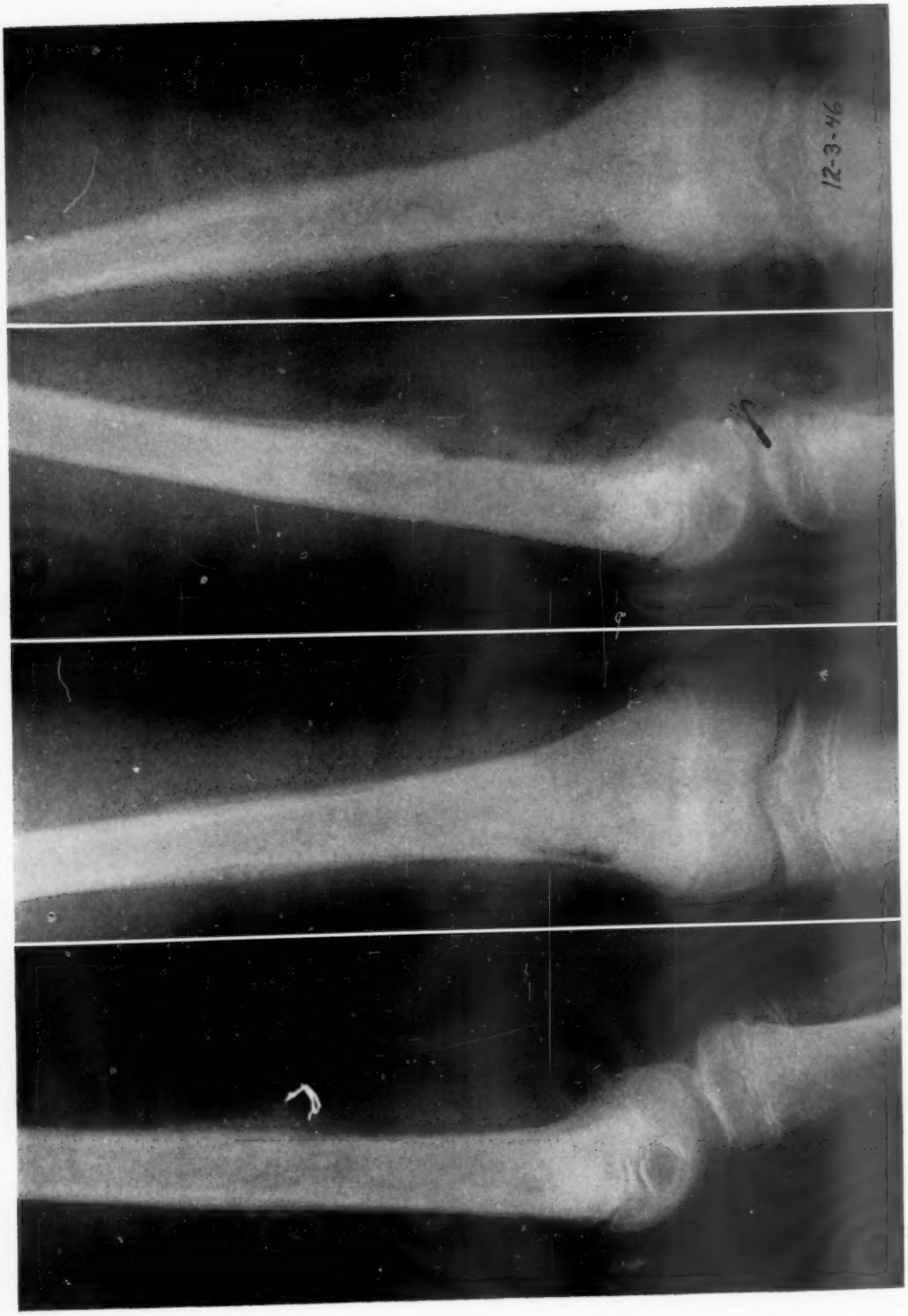


Fig. 5.—Clinical chart of girl, aged 11 years, whose femoral lesion was arrested by penicillin treatment (first case so treated in St. Joseph [Dr. Timmerman]).

PROGRESSIVE GANGRENE

The importance of "mixed infection" had been emphasized for many years by Dr. H. W. Orr of Lincoln, Nebraska. The worst that can happen along this line is illustrated by the so-called bacterial synergistic progressive gangrene of the skin and subcutaneous tissues (Fig. 12, from Steindler's clinic at Iowa City; treated by the author and studied bacteriologically by E. Freund). This extensive and rapidly spreading infection was observed in an adult man following simple drainage of a flare-up osteomyelitis of the tibia. The man's life was undoubtedly saved by disarticulation of the extremity at the hip joint. Even



B.

A.

D.

C.

Fig. 6.—Same case as Fig. 5. Complete evolution and restitution of the nonsuppurative femoral lesion: *A*, Oct. 9, 1946—39 days after onset; *B*, Dec. 3, 1946; *C*, March 15, 1947; *D*, Feb. 10, 1951.

then, a single metastasis occurred after this operation to a rib which was controlled by surgical drainage. In both areas, the Staphylococcus and *Streptococcus hemolyticus* were constant bacteriologic findings in the tissues as well as in several experimental guinea pig passages. Also, in the experimental animals similar gangrenous infection was only produced when both organisms were injected into them simultaneously. The man recovered.

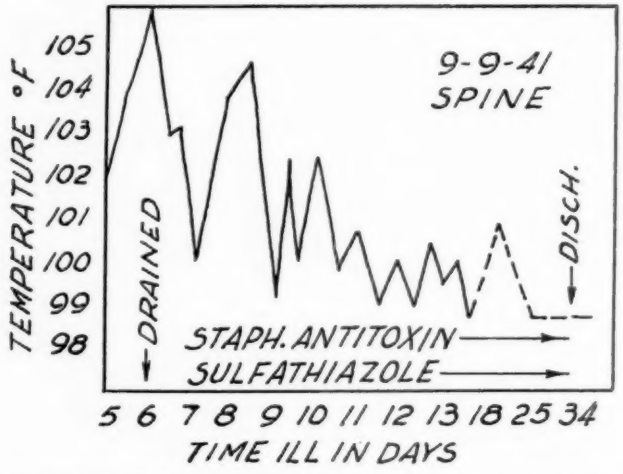


Fig. 7.—Clinical chart of boy, aged 17 years, with an acute osteomyelitis of the upper dorsal vertebrae (laminae, with epidural abscess) who was drained surgically on the sixth day of illness. He made a full recovery without further operative interference.

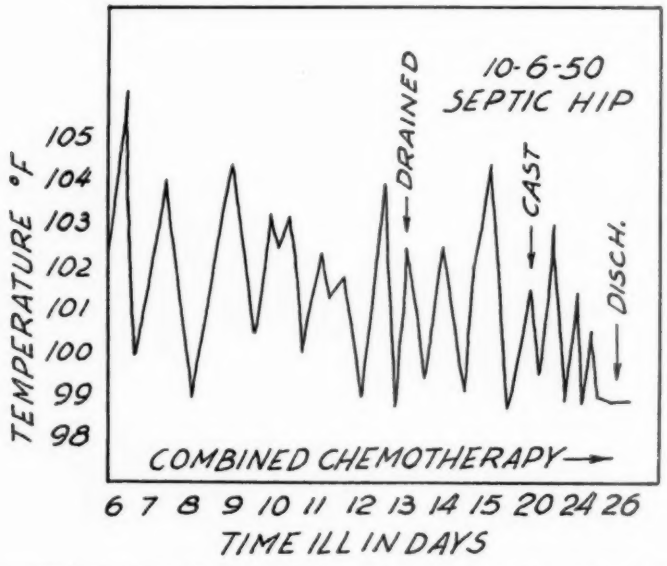


Fig. 8.—Clinical chart of girl, aged 6 years, with acute septic hip infection which was surgically drained on the thirteenth day of illness and put in a cast. Full recovery followed without further operative interference.

PRINCIPLES OF PRIMARY AND SECONDARY CONTROL

The schematic principles of management (Table II) are predicated upon the assumption that hematogenous pyogenic osteomyelitis is a self-limited disease and, therefore, is amenable first to expectant or medical treatment. There is

TABLE II. PRINCIPLES OF MANAGEMENT

	Bacteremia		
	SEEDING	FIXATION	RESULT
	Antigenic	Relative Immunity	Allergic
Fatal	Abortive	Arrestive Purulent	Sequestrum (fatal)
		Reversible	Irreversible
	PRIMARY CONTROL	SECONDARY CONTROL	
	Chemotherapy		
Fluids	Sedation	Drainage	Sequestrectomy
Blood	Traction or splinting, brace, cast		
Calories, vitamins, etc.			Orr method

no intent to relegate surgical care to a secondary place, but only to point out that operative restraint is indicated until definite suppuration is evident clinically. The effectiveness of chemotherapy has been most conspicuous in controlling the general infection and, hence, practically eliminating the most serious complications of a general infectious nature. This is also reflected in the minimal mortality rate.

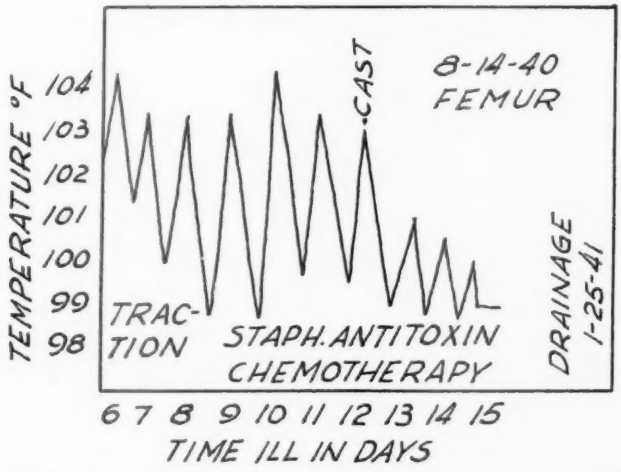


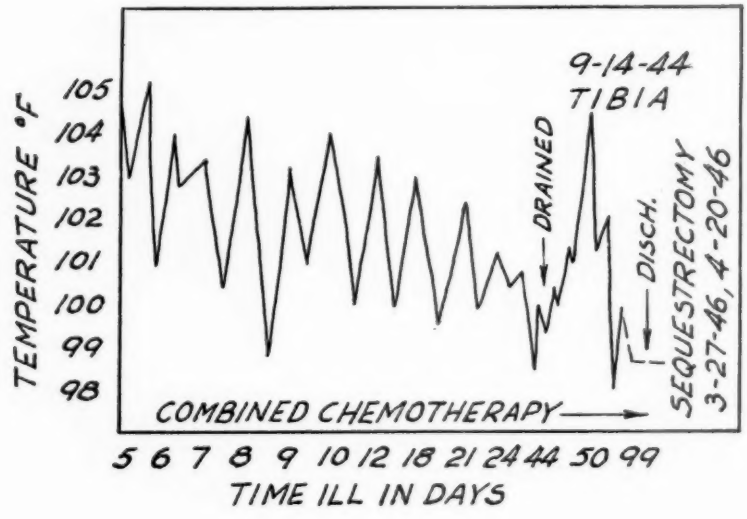
Fig. 9.—Clinical chart of girl, aged 11 years, with an osteomyelitis of the femur which was drained surgically over four months after onset although the abscess was evident shortly after onset of her illness. She was the earliest case treated with staphylococcus antitoxin (Lederle) and Neoprontosil (by the author). Operation was deliberately delayed in the hope that the abscess would clear up spontaneously, which it did not. The surgical implications are obvious. After operation the bony lesion resolved spontaneously (like that shown in Fig. 6, *A-D*).

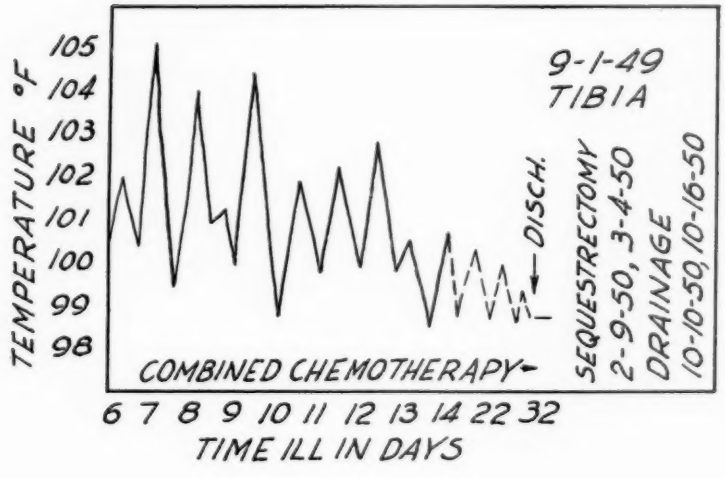
Unfortunately, the small number of resistant bacteria observed in the early days (about 5 per cent originally to penicillin) to the various types of chemotherapy is increasing at an alarming rate, another potent reason for reviewing basic principles of treatment. Along with chemotherapy every effort is made to increase the innate resistance of the patient to infection (and operative trauma, when indicated). The same holds true after surgical intervention. The importance of tremendous dosages of the various chemotherapeutic agents is now being appreciated. Dosages recommended only a few years ago now seem woefully inadequate.

Attention to the localization is focused by pain and muscle spasm. Suppuration may escape diagnosis unless aspiration is resorted to when local signs and symptoms develop. Sedation is always supplemented by mechanical meas-

ures aimed toward the comfort of the patient, especially when joints are actually or sympathetically involved. Bacterial fixation always increases the local picture of inflammation and is soon notable on x-ray films (paraosteal soft tissue changes occur first). This is shortly followed by patchy demineralization,

A.





B.

Fig. 10.—*A*, Clinical chart of girl, aged 11 years, with tibial osteomyelitis in whom simple drainage of abscess was not enough and had to be supplemented by sequestrectomy at a later date. *B*, Clinical chart of girl, aged 10 years, with tibial osteomyelitis, with similar clinical evolution and treatment.

periosteal reaction, and breaks in the cortex (in ten to fourteen days). Due to the lack of secondary infections, bone changes under chemotherapy are less marked than was formerly the case. There follows, rather than an extension of the disease, an absorption of an aseptic necrosis; recalcification proceeds without

extensive sclerosis; and, gradual restitution goes on as in the case of a bone graft. Also, sequestra are less extensive than formerly because of the absence (in most cases) of secondary infection or its minimization.

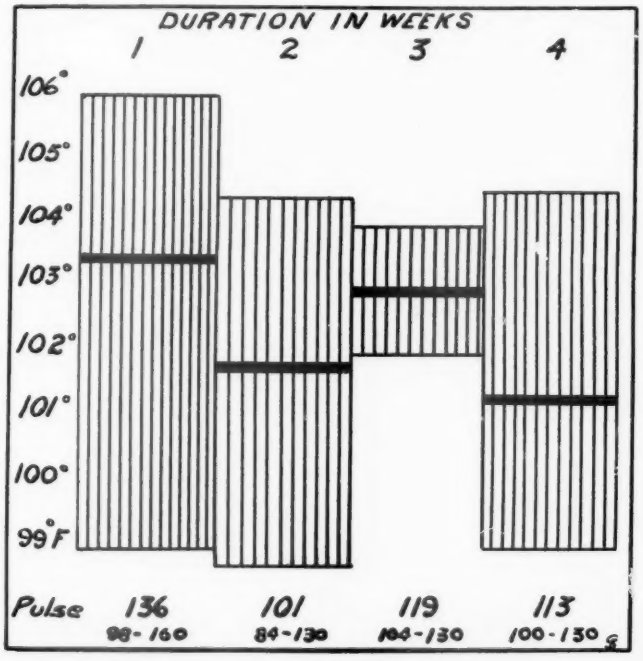


Fig. 11.—Temperature ranges and averages in a series of 72 cases of acute hematogenous pyogenic osteomyelitis as recorded on their respective hospital admissions. Results of operations are stated in Table I.

Fig. 12.—Picture of progressive gangrene in adult man following drainage of osteomyelitis (flare) of the tibia, due to so-called bacterial synergism and symbiosis.

When diagnostic uncertainty is provoked by these bone changes (especially when the case is seen later after onset for the first time), the dilemma may be resolved by further trial of provocative chemotherapy. Needle biopsy (or even open ones) may be resorted to in cases of real doubt.

In contrast to this situation, abscess formation clinches the diagnosis of osteomyelitis. There should be no hesitancy in operative drainage when this has occurred, although some surgeons are recommending repeated aspirations in respect to joint infections. The latter is most suitable in young children (streptococcal). Direct operations on the bone lesions themselves are reserved only for the chronic stages when definite and obvious deep-seated infections are present. For all operative interventions, I prefer the Orr method.

CONCLUSIONS

Chemotherapy has contracted the clinical life history of hematogenous osteomyelitis (pyogenic) to a small but definite grouping of cases in which medical and surgical treatment may be integrated to a very high level of effectiveness. Two critical areas occur in the evolution of the disease under chemotherapy, that is, suppuration and exfoliation of bone. The latter has no operative significance unless it is accompanied by suppuration. Operation is always delayed, in any case, until frank suppuration is evident clinically.

Two salient developments twenty years ago brought the clinical life history of hematogenous pyogenic osteomyelitis into a clearer focus and understanding: the principle of delayed operative interference, and, later, chemotherapy for the control of the general infection and hence the most dreaded of its complications.

EXPERIMENTAL RECONSTRUCTION OF THE TRACHEA WITH BLADDER MUCOSA

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IN reconstruction of the trachea with living tissues there are two major problems. An epithelized tube must be formed, and this tube must be provided with a supporting structure strong enough to resist the negative and positive intratracheal pressures without collapsing or leaking. Morfit and his associates[7] have reviewed previous attempts at reconstruction and substitution. Huggins[3] demonstrated, in 1930, that bladder mucosa implanted in connective tissue would become surrounded by bone. This has been repeatedly confirmed.[2, 4-6] These experiments were designed to explore the usefulness of bladder mucosa in tracheal reconstruction.

METHODS AND RESULTS

Mongrel dogs, maintained in an air-conditioned kennel and fed on Purina dog chow, were used. Autogenous bladder mucosa was obtained as follows. The base of the bladder was closed with a heavy silk tie. Sterile saline solution was injected into the bladder through a fine needle. The detrusor muscle of the distended bladder was split down to the mucosa. With careful sharp dissection and traction on the detrusor muscle, an intact sheet of mucosa measuring several centimeters on a side was removed. The tie at the base of the bladder was removed, a cystostomy tube was sutured in place, and the bladder was sutured to the anterior abdominal wall. The dogs usually pulled out the polyethylene cystostomy tube in approximately a week.

Eight dogs were used to test the ability of bladder mucosa to replace a small defect in the trachea. The cervical trachea was exposed and a 3 by 3 cm. window removed from the anterior surface. A sheet of bladder mucosa was sutured over this defect. In 4 dogs, the mucosal surface was placed facing toward the lumen and, in the other 4, facing away from the lumen.

Table I shows the results in this group. The 3 dogs which died at 2, 13, and 18 days showed no evidence of bone formation. Those which survived 75 days or more with the mucosal surface facing away from the lumen, showed good bone formation. A well-formed plaque of bone, 2 to 3 mm. thick, with

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definite marrow elements bridged the defect. The lumen was lined with an intact layer of metaplastic epithelium (Fig. 1). When the mucosa was implanted with its surface facing the lumen, epithelium was present but there was no bone formation (Fig. 2).

In the second group (7 dogs), sections of the cervical trachea from 5 to 12 cm. in length were removed and replaced by a polyethylene stint. Bladder mucosa was wrapped around this stint with the mucosal surface facing away from the lumen. The mucosa was sutured to the stint and to the severed ends of the trachea, using 3-0 chromic catgut.

TABLE I*

DOG NUMBER	SURVIVAL DAYS	MUCOSA FACED	BONE	EPITHELIUM
X 5	13	In	0	3+
X 0	330	In	0	3+
X 47	360	In	0	3+
X 55	2	Out	0	Graft present
X 208	18	Out	0	0
X 97	75	Out	3+	3+
X 182	180	Out	3+	3+

*Dogs in which window defects were created and covered with free grafts of bladder mucosa, some with the mucosal surface facing away from the lumen and some with the mucosal surface facing toward the lumen.

(A) For Epithelium.
1+ = Islands of epithelium up to 50 per cent coverage.
2+ = More than 50 per cent coverage.
3+ = Complete (100 per cent) coverage.

(B) Bone Formation.
1+ = A single island of bone.
2+ = Scattered islands of bone.
3+ = Sheet of bone practically encircling the trachea.

The results in this group of sleeve reactions are shown in Table II. The polyethylene stints sutured with catgut became loose and were aspirated into the bronchial tree with collapse of the defect and strangulation of the dogs. The mucosal transplants failed to become fixed to the surrounding tissues and grow because of the movement of the trachea and stint. Two dogs showed a very small amount of bone formation. A granulation-lined tract remained.

TABLE II*

DOG NUMBER	SURVIVAL (DAYS)	MUCOSA FACED	BONE	EPITHELIUM
X 87	6	Out	0	0
X 62	14	Out	0	0
X 228	20	Out	+1	0
X 333	20	Out	0	0
X 229	20	Out	0	0
03-85	22	Out	0	0
X 149	60	Out	+2	0

*Dogs in which a sleeve resection of the trachea was bone and the defect filled with a polyethylene stint covered with bladder mucosa. The mucosa was sutured to the stint.

Because of these poor results a different operative procedure was used in the next series (5 dogs), with sleeve resections. After resection of the segment of trachea the tract was lined with a sheet of bladder mucosa which was sutured to the muscle and connective tissue with interrupted catgut sutures. The sheet was perforated with many small incisions. A polyethylene stint was fixed in place with fine steel wire. The muscle and connective tissue with their investing layer of bladder mucosa were closed firmly around the stint.

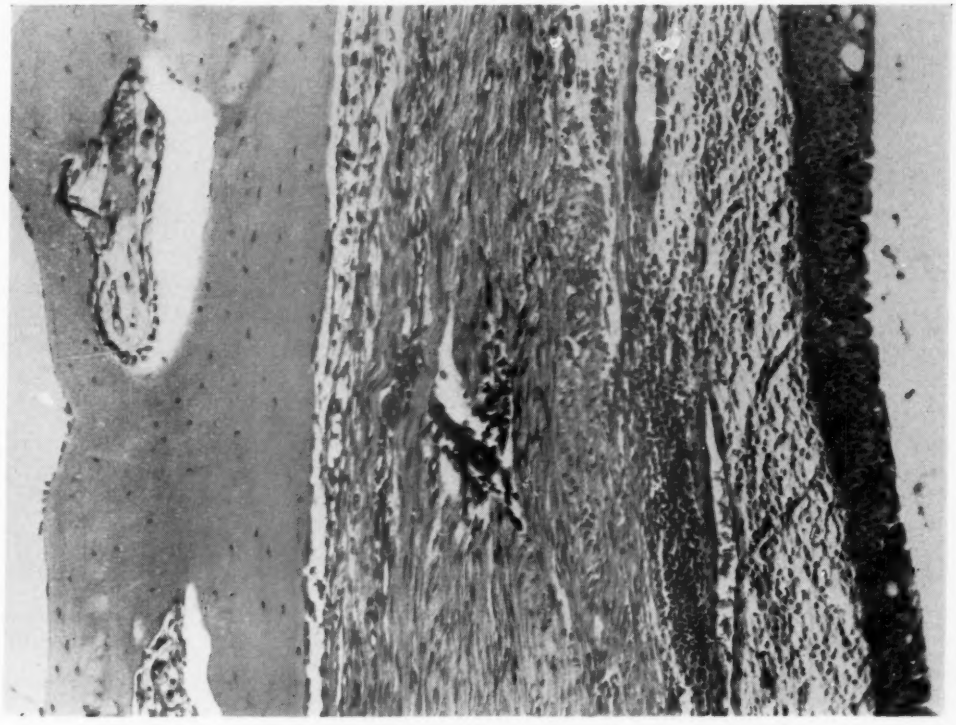

Fig. 1.—Photomicrograph of the tracheal graft in Dog X182. The mucosa is transitional in type and the bone is quite mature.

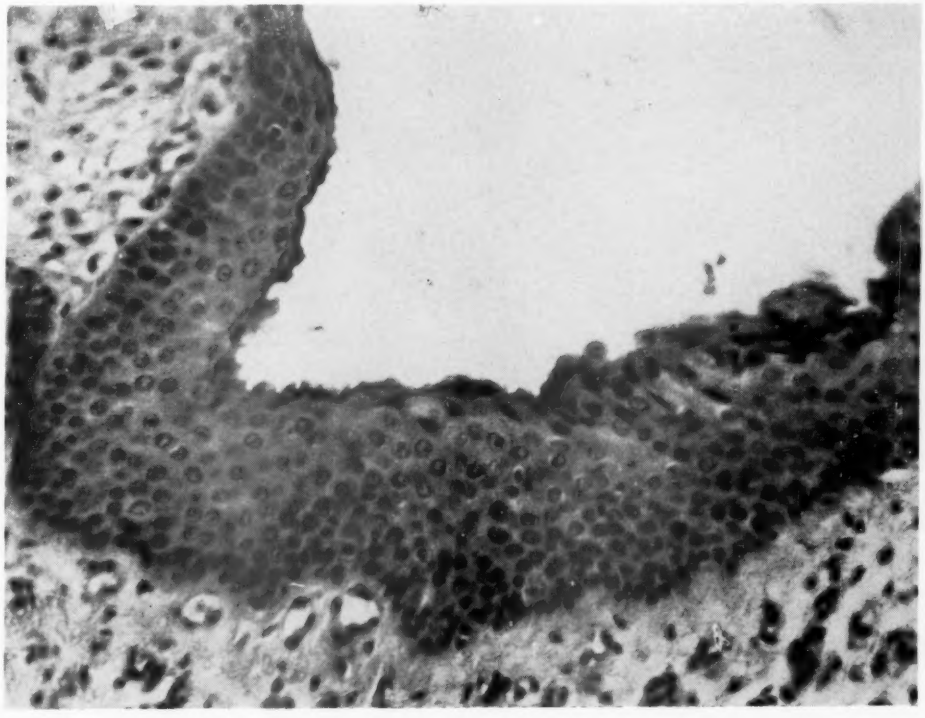

Fig. 2.—Photomicrograph of a section of the graft in Dog X47. The epithelium is metaplastic squamous. No bone elements were seen.

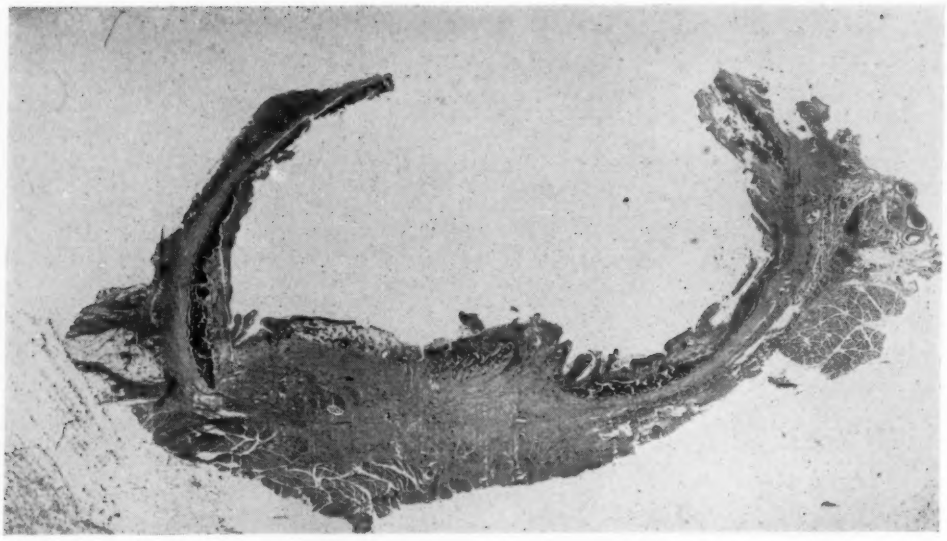

Fig. 3.—Photomicrograph of a cross section of the reconstructed area in the trachea of Dog 295, sacrificed three months after the trachea was completely replaced by bladder mucosa. The resulting bone formation encircles the entire lumen.

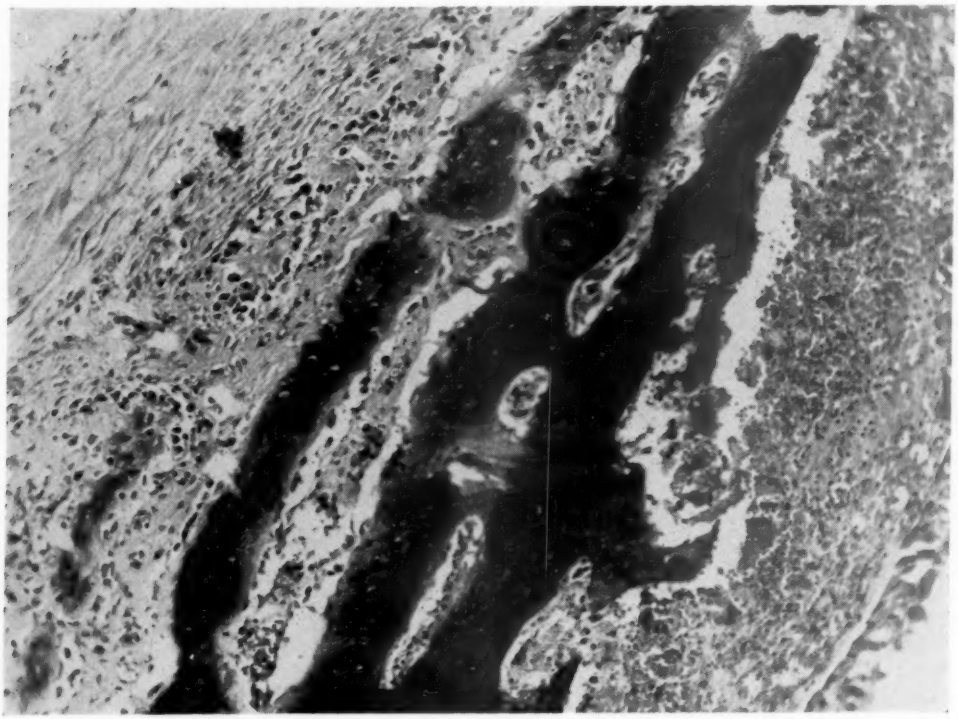

Fig. 4.—Photomicrograph showing the bone formation in the reconstructed trachea of Dog 295. Mature bone is present with marrow elements. The mucosa appears transitional.

Bone and epithelium were found in the 4 animals in which the mucosa had been turned outward. In the two best results, the entire lumen was almost surrounded by a thin sheet of bone (Fig. 3). Following removal of the stint after three months these dogs had an adequate airway and no stridor. However, marked edema of the submucosal layers developed later, with death of one dog in 48 hours and of the other in 24 hours, caused by obstruction of their airway. In the one dog in which the mucosa was faced into the lumen, mucosa was present but there was no bone formation and the trachea collapsed immediately after removal of the stint.

TABLE III*

DOG NUMBER	SURVIVED DAYS	CAUSE OF DEATH	MUCOSA FACED	BONE	EPITHELIUM
34	60	Sacrificed	Out	2+	2+
666	75	Sacrificed	Out	2+	3+
277	90	Sacrificed	In	0	3+
273	105	Edema in trachea after stint removed	Out	3+	3+
295	105	Edema in trachea after stint removed	Out	3+	3+

*Dogs in which a sleeve resection of the trachea was done and replaced with a polyethylene stint covered with bladder mucosa. The mucosa was sutured to the surrounding connective tissue.

DISCUSSION

The unusual potential of bladder mucosa to produce ossification in connective tissue has interested a number of investigators. The limited ossification may be inadequate for larger structures but is quite sufficient for the replacement of tracheal rings. As our data demonstrate, it is possible to induce ossification about the bed of the cervical trachea using bladder mucosa.

Although the bladder mucosa was implanted with the mucosal surface facing away from the lumen, the tract developed a complete epithelial lining. This lining was metaplastic, resembling transitional, squamous, and respiratory epithelium at different points so that it was difficult to determine its origin. Morfit[7] noted that respiratory epithelium grew only a few millimeters into the tract which remained, following a sleeve resection of the trachea, and that the majority of the area remained covered with granulation tissue as long as a year after resection. It may be that in our cases, the more rigid support of bone about the tract provided a better bed for the epithelium or that bladder epithelium grew back through the perforations in the sheet of bladder mucosa.

The chief problem that remains to be dealt with is the marked edema in the submucosal layers which develops when the polyethylene stint is removed.

SUMMARY AND CONCLUSION

1. Using mongrel dogs, window and sleeve defects in the trachea were replaced with autogenous bladder mucosa.

2. When the bladder mucosa was placed with the mucosal surface away from the lumen it was possible to induce a satisfactory supporting structure of bone in the surrounding connective tissue. In addition, the tract became epithelized with a metaplastic epithelium.

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Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

A COMPARISON OF CARDIOJEJUNOPEXY WITH OTHER METHODS OF REVASCULARIZING THE HEART

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INTRODUCTION

CORONARY artery disease offers a challenge to physicians as a whole and to men interested in research in particular. Though the disease has been recognized for over forty years, little advance has occurred in its treatment.[39, 57] The fatality rate of individuals with infarction is high.[28, 33, 43] Of 488 persons with myocardial infarction, 25 per cent are dead in two months, 50 per cent are dead in one year, and 75 per cent are dead in three years.[33] In addition, the incidence of coronary artery disease is constantly increasing due to the gradually lengthening life span of the population. Since the first description of coronary thrombosis by Herrick,[29] forty-three years ago, many attempts have been made to decrease the pain of the disease and improve the blood supply to the heart.

Perhaps the first indication that it might be possible to improve the blood supply of the heart was the work by Hudson[31] in 1932. He demonstrated extensive extracardiac anastomoses of the coronary arteries and, later the same year, with Mautz, demonstrated an increase in these anastomoses with pericarditis.[38] The following year, Beck reported on the possibility of bringing additional blood to the heart from an outside source. He further postulated that flow would be toward the heart if the coronary flow was impaired.

Since the first experiments of Beck, the attempts at improving the heart's blood supply have fallen into three main types. In the first type, a tissue graft such as lung or omentum is applied to the heart. The second type of operation is designed to stimulate increased intercoronary anastomoses by

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methods such as the instillation of talc in the pericardium. In the third type, vascular communication is produced between the heart and the aorta or systemic vessels.

Beck became a leader in the use of tissue grafts. Beck, Feil, and Griffith,[6, 7, 8, 20, 24] from 1935 to 1938, reported on the use of pedicled muscle grafts from the pectoralis. Later, he mentioned using several other types of tissues, including mediastinal fat, parietal pericardium, and spleen.[10] Apparently none of these grafts were very successful since no further reports were made on them.

O'Shaughnessy[17, 40, 41, 42] pioneered in the use of an omental graft to the heart. In 1936, he demonstrated that dogs with an omental graft were protected from death when the anterior descending artery was occluded. He also showed communication between the omental vessels and the heart by means of India ink.

In 1949, Carter published a re-evaluation of the cardiopneumopexy and quoted the work of Lezius on cardiopneumopexy in dogs. For these experiments, there is no evidence that barium could be injected into the vascular supply of the graft and arrive in the heart muscle.

The use of bowel to revascularize the heart has been reported on by Baronofsky, Sprafka, and Noble[2] and by Key and Kergin.[34] The former group used a closed bowel technique while the latter used an open technique. The first to demonstrate the improved intercoronary anastomoses produced by pericardial adhesions were Beck and Tichy.[4, 10, 22] They produced the adhesions by removing the epicardium with a mechanical burr.[49] In 1942, Thompson[50, 51, 52, 53] reported success in producing pericarditis with the use of talc rather than a burr. He had no mortality in dogs with occlusion of the anterior descending artery following the production of a talc pericarditis. In addition to talc, sand, aleurnot, and asbestos have been used. Actually, it has never been demonstrated that the pericarditis varies regardless of the type of material inserted into the pericardium.

Coronary sinus ligation probably causes increased intercoronary anastomoses. Some of the first work on this operation was done by Robertson[48] and Gross.[12, 25, 26] Thornton has stated that the increased venous pressure within the coronary sinus returned to normal in one month[35] suggesting that any value the procedure has is not on the basis of elevated venous pressure. Fauteux[18, 19] also worked with coronary sinus occlusion and, in 1940, showed that dogs having a previous ligation of the coronary sinus were protected from death with anterior descending artery occlusion.

This paper is a study of the effectiveness of several methods of revascularization, especially cardiojejunopexy. The work on cardiojejunopexy stems directly from the initial work in 1954 on the use of intestinal grafts to the heart by Baronofsky, Sprafka, and Noble.[2]

METHODS AND MATERIALS

Cardiojejunopexy was performed as previously described in two stages (Figs. 1 and 2).[2] Seventy-three dogs were prepared in this manner. A control group of 84 dogs was also used. Fifty-three of these 84 had no previous

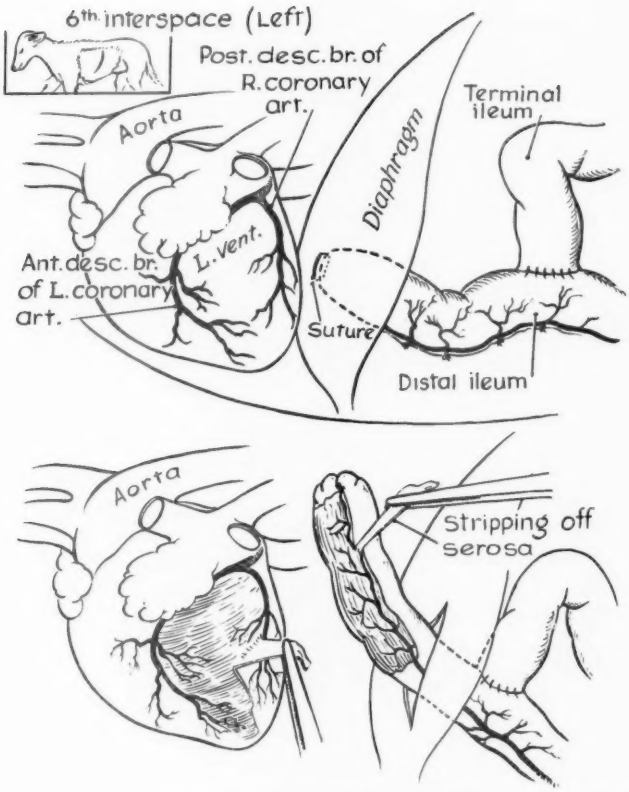


Fig. 1.—First stage in cardiojejunopexy utilizing the Roux Y method of restoring intestinal continuity. The epicardium of the heart and the serosa of the bowel are the shaded areas.

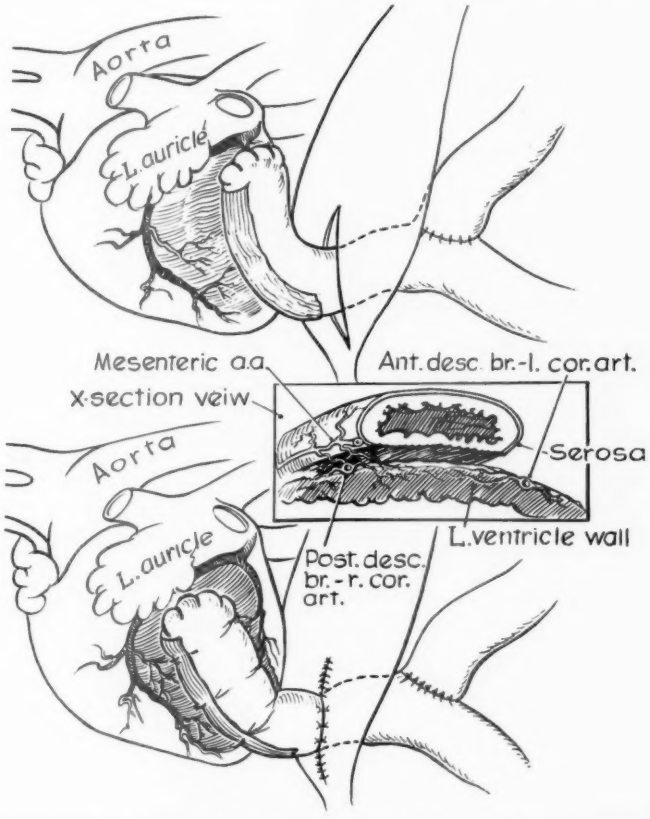


Fig. 2.—Suturing of intestine to heart in second stage of cardiojejunopexy. Insert shows cross section.

revascularization procedures attempted; and 31 were divided into four groups, each with a different type of revascularization as follows. A group of 8 dogs was prepared by instilling talc in the pericardial sac. In 5 of the dogs, the epicardium was stripped over the left ventricle before the instillation of talc.

A group of 9 dogs was prepared with an omental graft to the heart. The left sixth interspace was opened and omentum was drawn up into the chest through a small opening in the diaphragm. After the pericardium was opened, the epicardium was stripped over an area between the anterior descending artery and the circumflex artery. The omentum was sutured to the heart over this area. The pericardium was loosely closed around the omentum.

A third group of 8 dogs was prepared with cardiopneumopexy. In these dogs, the left fifth intercostal space was opened. The pericardium was opened and the epicardium stripped as before, but the pleura could not be stripped from the lung. The upper portion of the lower lobe was then sutured to the heart with mattress sutures. The pericardium was left open.

A final group of 9 dogs was prepared with coronary sinus ligation. The right fourth intercostal space was entered and the pericardium opened. Then, two 2-0 silk sutures were tied around the coronary sinus.

Coronary artery occlusion was then produced in the dogs with cardiojejunopexy and the control dogs, including those in the four subgroups with other types of revascularization to study the effectiveness of the revascularization.

The coronary arteries were occluded in stages by means of a Goldblatt clamp[11, 13, 16, 37, 44] (Fig. 3). Clamps were placed on the anterior descending and/or circumflex arteries at their origin[6] (Fig. 4) and tightened so as to partially occlude either one or both arteries. The clamps were placed about the arteries within 5 mm. of their origin from the aorta. The small foot plate in the base of the clamp was removed, the clamp placed about the vessel, and the foot plate reinserted. Then, with forceps holding the clamp, a screw driver was used to tighten the clamp. The right coronary artery was occluded acutely by a tie. Finally, in all dogs after each occlusion, the remaining patent coronary arteries were occluded in stages. In other words, an animal surviving all of these operations would have essentially the normal coronary blood supply occluded.

Nineteen dogs with cardiojejunopexy and 20 control dogs had occlusion of the anterior descending artery in two stages three to four weeks apart. Those dogs surviving had occlusion of the right coronary artery acutely in one month. Finally, in the survivors, the circumflex artery was occluded in two operations one month apart.

A similar comparison was carried out between 19 cadiojejunopexy dogs and 19 control dogs with the exception that the circumflex, right, and then the anterior descending arteries were occluded in that order.

The last group compared were 32 dogs with cardiojejunopexy with 46 control dogs. The control dogs were broken down as follows: 14 dogs had no

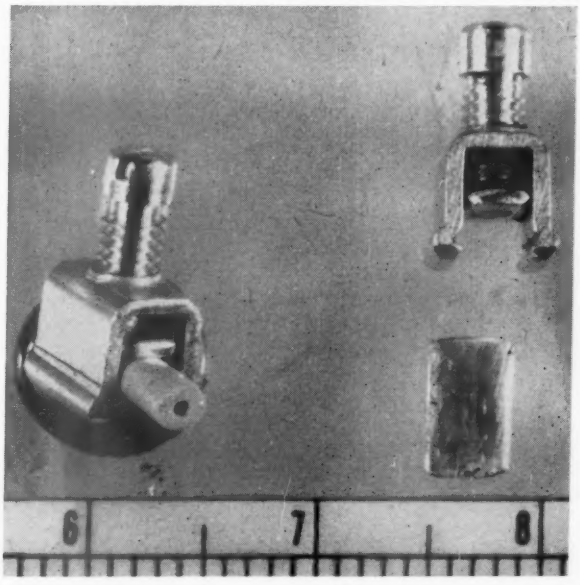


Fig. 3.—Goldblatt clamp used in occluding the arteries in two stages.

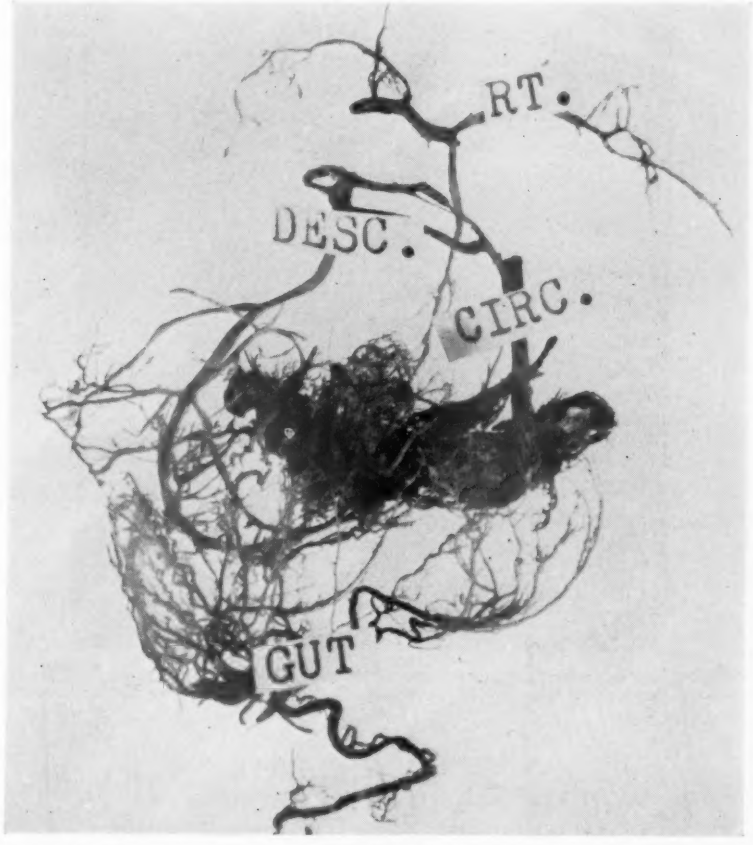


Fig. 4.—Injection of coronary arteries with plastic material via mesenteric artery.

previous revascularization; 9 had instillation of talc into the pericardial sac; 8 had ligation of the coronary sinus; 6 had cardiopneumopexy; and 9 had cardio-omentopexy.

These dogs had partial occlusion of both the anterior descending and the circumflex arteries at the initial operation. Then in one month, the circumflex artery was completely occluded. In one more month, the survivors had ligation of the right coronary artery. Finally, in all survivors, the anterior descending artery was completely occluded.

Fig. 5.—Injection of coronary arteries with cinnabar via the mesenteric artery. Lower portion of photograph shows gut as it extends onto heart. A clamp has been placed on the anterior descending artery.

Before and after operation, electrocardiograms were taken with the electrodes placed according to the method of Kimura.[32]

When dogs with cardiojejunopexy, cardio-omentopexy, and cardiopneumopexy died or were sacrificed, the hearts were studied by injection of the grafts with India ink and barium sulfate. Injection was carried out through

an artery of the graft. Positive injection consisted in getting India ink out of the coronary sinus or coronary artery orifices and barium out of the coronary ostia. X-rays were taken as a final check on the amount of barium in the coronary artery.

Coronary arteriograms[36] were obtained by injecting about 4 c.c. of Urokon into the aorta just above the aortic valves through a catheter inserted into the carotid artery in the neck. The tip was located by fluoroscopy. A relay was used which triggered the x-ray machine and was set off by the injecting syringe.[36] This system made it possible to get a satisfactory arteriogram with the exposure of only one film. The simplicity with which arteriograms were obtained using this relay system was in marked contrast to difficulties encountered when the Sanchez rapid-changing cassette was used. Studies of the electrocardiographic response to hypoxia were carried out in dogs with no previous surgery, dogs with one or more of the coronary arteries partially or completely occluded, and dogs with cardiojejunopexy with one or more coronary arteries partially or completely occluded. Each dog was anesthetized and placed for fifteen minutes on an automatic respirator breathing room air. Then, after an electrocardiogram was taken, the dogs were respired on 10 per cent oxygen for ten minutes, and a second electrocardiogram was taken.[27]

Injections with plastic and cinnabar were carried out in the cardiojejunopexy dogs by injection of the artery of the graft to outline the coronary arteries. The final study carried out on all hearts was the examination for infarcts when the dogs died or were sacrificed.

RESULTS

The mortality rate with anterior descending artery occlusion in control dogs was 70 per cent, and in the cardiojejunopexy, only 21 per cent (Table I). The mortality rate with circumflex coronary occlusion in the control group was 63 per cent, and in the group with cardiojejunopexy, only 21 per cent (Table I). In the group of dogs with occlusion of the right coronary artery, the control group had a mortality rate of 50 per cent, and the cardiojejunopexy dogs had a mortality of 12 per cent.

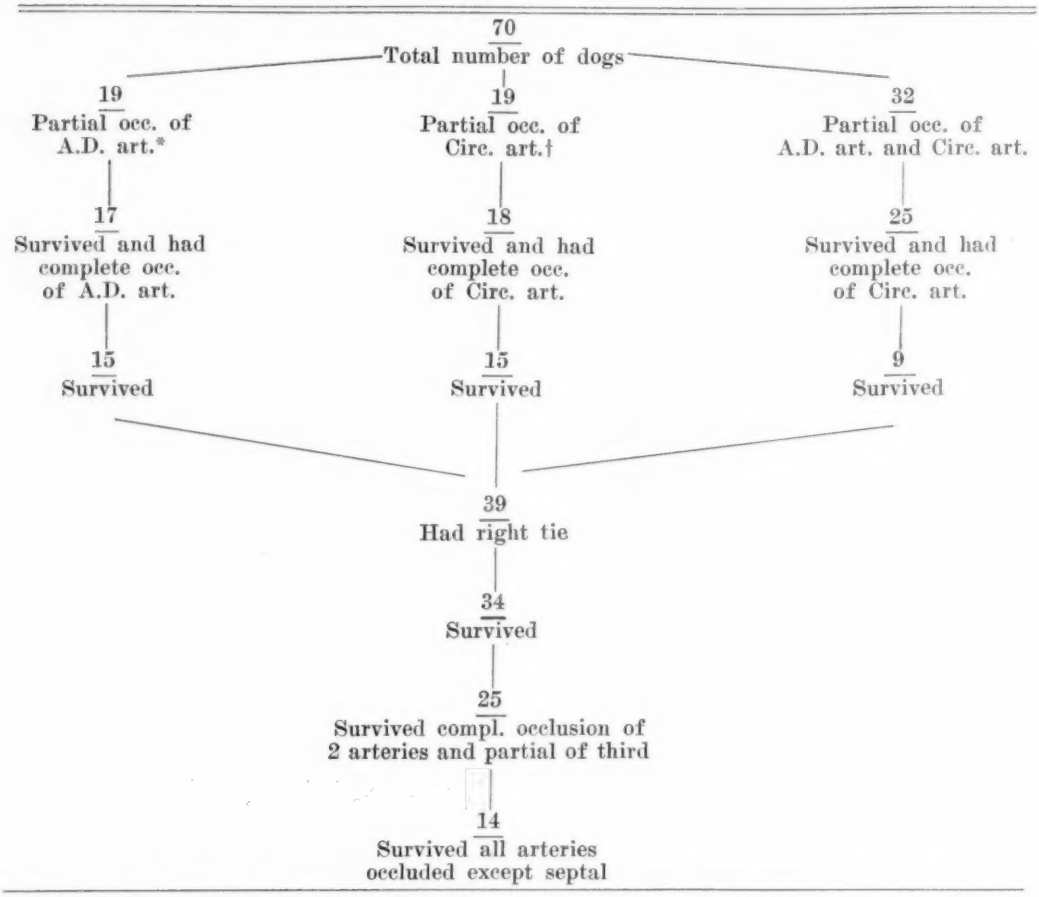
TABLE I. MORTALITY RATES FOR OCCLUSION OF SINGLE CORONARY ARTERY

	NO. OF DOGS	DEATHS	M. R.* (%)
Occlusion of Anterior Descending Artery			
Cardiojejunopexy	19	4	21
Controls	20	14	70
Occlusion of Circumflex Artery			
Cardiojejunopexy	19	4	21
Controls	19	12	63
Occlusion of Right Coronary Artery			
Cardiojejunopexy	39	5	12
Controls	18	10	55

*Mortality rate.

Tables II and III are a graphic summary of the mortality rates in all of the groups. The control series included the dogs with no revascularization

TABLE II. HEART VASCULAR SERIES (CARDIOJEJUNOPEXY)



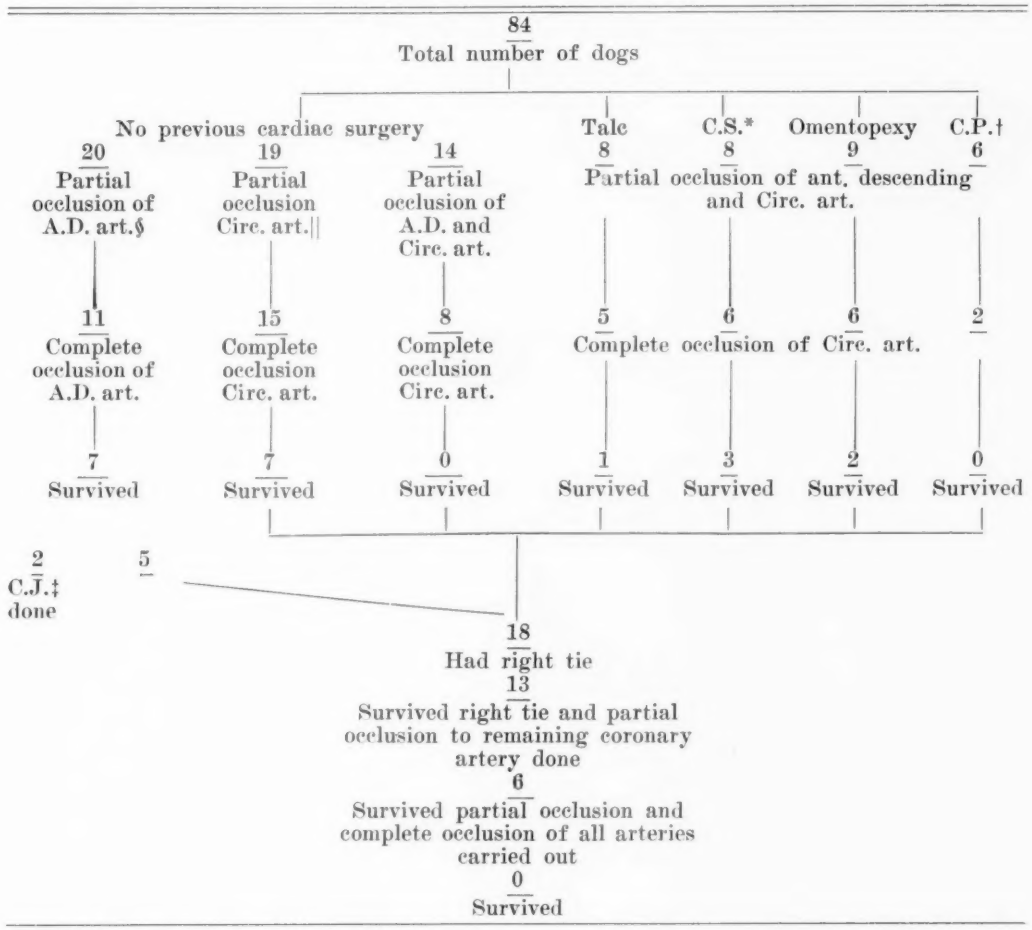
*A.D. art.: Anterior descending artery.
†Circ. art.: Circumflex artery.

procedures and also the groups with talc, coronary sinus ligation, omentopexy, and cardiopneumopexy. Fourteen dogs with cardiojejunopexy survived occlusion of most of their normal coronary blood supply, but none of the control dogs were able to survive this degree of coronary artery occlusion.

Injections of the mesenteric artery with plastic or cinnabar revealed the a successful injection with India ink in 86 per cent and with barium in 70 per cent (Table VI). A positive injection consisted in getting India ink out of the coronary sinus or coronary artery ostia or barium out of the coronary artery ostia when these substances were injected into the artery of the graft. The omentopexy dogs were next best with 77 per cent and 55 per cent, respectively, and the poorest were the cardiopneumopexy dogs. It was possible to get positive injections with barium in the cardiojejunopexy dogs in about 70 per cent regardless of the age of the graft (Table VI).

Injections of the mesenteric artery with plastic or cinnebar revealed the extensive communications which were present between the graft and the heart (Fig. 4).

TABLE III. CONTROL SERIES



*C.S.: Coronary sinus ligation.
†C.P.: Cardiopneumopexy.
‡C.J.: Cardiojejunopexy.
§A.D. art.: Anterior descending artery.
‖Circ. art.: Circumflex artery.

TABLE IV. INFARCTS FOUND WITH ONE CORONARY ARTERY COMPLETELY OCCLUDED

	ANTERIOR DESCENDING		CIRCUMFLEX		RT. COR. ARTERY	
	C. J.	CONTROL	C. J.	CONTROL	C. J.	CONTROL
Number of dogs	11	13	14	9	12	15
Infarcts	2	12	4	8	2	14
Per cent of hearts with infarcts	18	90	25	88	16	93

TABLE V. ELECTROCARDIOGRAPHIC CHANGES IN DOGS UNDER CONDITIONS OF HYPOXIA AND REDUCED CORONARY ARTERY FLOW

	NUMBER OF DOGS	NUMBER SHOWING NO S-T OR T WAVE	PER CENT
Stock dogs	19	17	89
Control dogs	18	5	22
Cardiojejunopexy	17	10	58

Stock dogs: Unoperated or no cardiopulmonary surgery.
Control dogs: Have one or more coronary arteries partially or completely occluded.
Cardiojejunopexy dogs: Have had cardiojejunopexy and one or more coronary arteries partially or completely occluded.

TABLE VI

INJECTION STUDIES			
	NO. OF DOGS	NO. AND PER CENT POSITIVE INJECTION WITH INDIA INK	NO. AND PER CENT POSITIVE INJECTION WITH BARIUM
Cardiojejunopexy	81	74 (86%)	
	71		49 (70%)
Cardiopneumopexy	8	4 (50%)	
Omentopexy	9	7 (77%)	5 (55%)

PERCENTAGE POSITIVE INJECTIONS AT DIFFERENT AGES OF GRAFTED CARDIOJEJUNOPEXY		
AGE OF GRAFT	NUMBER	POSITIVE BARIUM INJECTIONS
10 days or under	3	1 (31%)
4-8 weeks	47	31 (65%)
6-12 weeks	11	8 (72%)

When the electrocardiograms were compared, the dogs with cardiojejunopexy showed no change in the S-T segments in 38 to 45 per cent of the group. The control group, however, showed no changes in the S-T segments

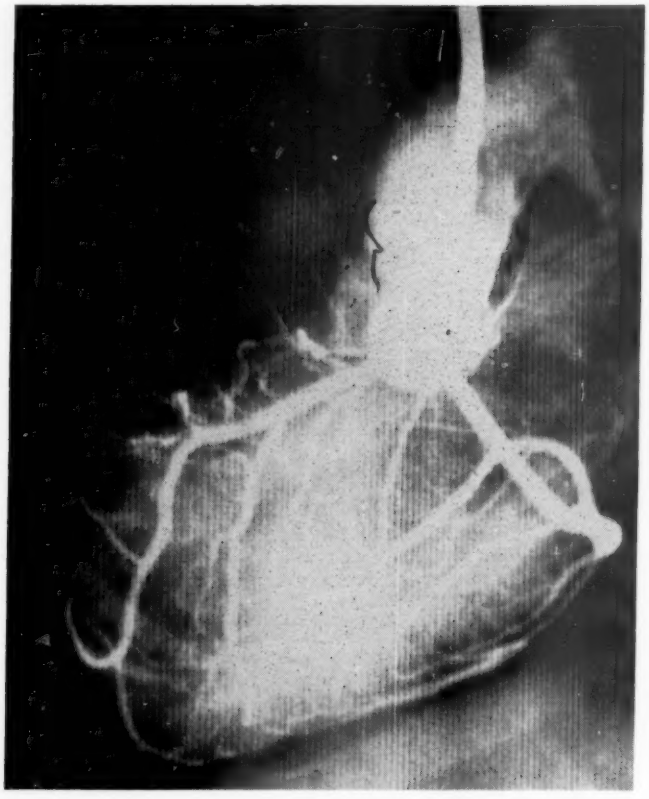


Fig. 6.—Normal coronary arteriogram.

in only 14 to 25 per cent of the group. When the electrocardiographic changes are evaluated statistically, there are only 5 chances in 10,000 that the result could have occurred by chance. (Table V.)

Coronary arteriograms on a group of 15 dogs with occlusion of the coronary arteries confirmed the fact that the particular artery remained occluded

in all instances (Figs. 6, 7, 8, and 9). Table IV shows the protection from infarcts which is afforded the dogs with cardiojejunopexy as compared to the controls.

DISCUSSION

It was not possible to go through this study without developing a firm conviction that the dogs studied were protected from myocardial infarction by having intestine sutured to the heart. The protection was made manifest by the decreased mortality rates and the reduced number of infarcts in the cardiojejunopexy dogs. The marked difference in mortality rates with right and

Fig. 7.—Coronary arteriogram showing circumflex artery occluded and anterior descending patent.

left coronary artery occlusion with a significantly lower rate when the right artery was occluded is probably a reflection of the lesser amounts of blood flowing through the right coronary artery. The injection with India ink[23] and barium of the various grafts applied to the heart offers an excellent opportunity to study vessels communicating between the graft and the heart. India ink will flow through vessels of any size. Barium, however, because of its particle size, will only pass through vessels which are arteriolar in size or

Fig. 8.—Coronary arteriogram showing anterior descending artery occluded and circumflex patent.

Fig. 9.—Coronary arteriogram showing anterior descending artery, circumflex and right coronary occluded.

Fig. 10.—Cross section of heart of dog surviving occlusion of all three coronary arteries except septal. No infarct present.

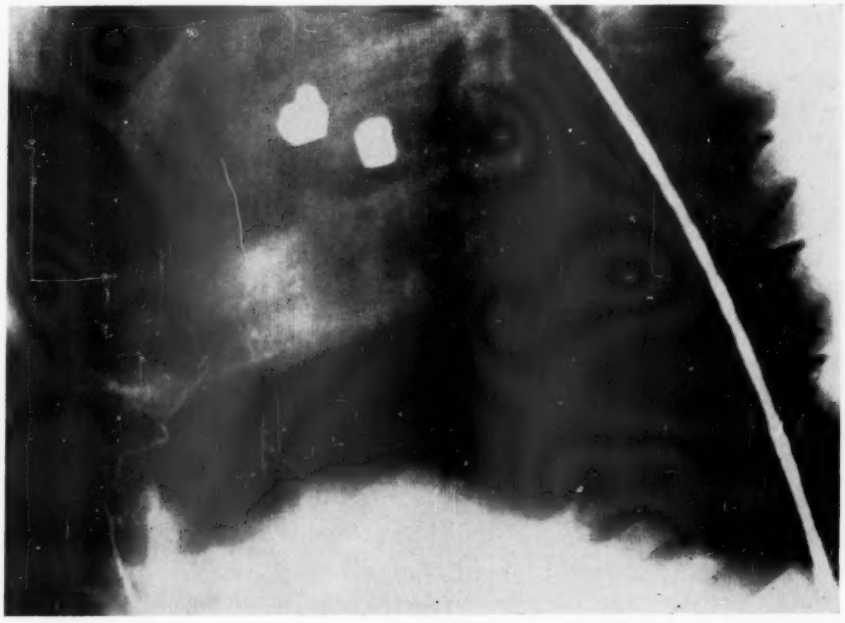


Fig. 11.—Injection of mesenteric artery with Urokon with filling of artery of intestine on heart.

larger.[5, 10] One of the criticisms of any grafting procedure has been that scarring between the graft and the heart would, after a few months, obliterate any vessels of arteriolar size. This is very definitely not the case with cardiojejunopexy as the percentage of positive injections is still 72 per cent in the dogs that have had the intestinal graft in place up to twelve months. This is in marked distinction from the results with aortic coronary sinus grafts which apparently lose contact with the capillary bed in about 2 months due to thickening of the endothelium secondary to the pressure.[1] It is interesting to note that in the cardiojejunopexy dogs barium injections were consistently positive regardless of the age of the graft. This seems to be quite conclusive proof that the healing of the graft does not occlude the vessel traveling between the graft and the heart.

Cardiojejunopexy apparently exerts protective action when any one of the three major coronary arteries is occluded. In fact, in some instances, cardiojejunopexy dogs with all arteries occluded except the septal showed no evidence of infarcts. This did not occur with any other procedure. The fact that it is possible to occlude all the coronary arteries except the septal would seem to indicate that blood must be brought to the heart through the graft. When the superior mesenteric artery was occluded for thirty minutes in dogs with all arteries occluded, however, no definite EKG evidence of infarct developed. This surprising finding would make one think that perhaps the intestine acts as a bridge for vessels in the mediastinum instead of being the primary source of the blood.

Many attempts have been made to demonstrate blood flow from a graft to the heart. We attempted on several occasions injecting Urokon into the mesenteric artery and taking x-rays of the heart. We were not able to demonstrate Urokon in the heart but showed that it quickly filled the artery supplying the limb of intestine on the heart (Fig. 11).

This might mean that the dye goes across into the heart, but the runoff into the coronaries is so rapid that the concentration in any one coronary is not high enough to allow visualization.

SUMMARY

Much work remains to be done on the problem of coronary artery disease. Changes in the diet may some day make it possible to eliminate completely arteriosclerosis. Until that time, procedures which show a definite protection from death in the presence of coronary occlusion should be carefully evaluated. Cardiojejunopexy shows this protection definitely in the research laboratory. The exact mechanism of the protection is not apparent.

The use of staged occlusion of the coronary arteries with the Goldblatt clamp is a valuable test of the effectiveness of any revascularization procedure. It is certainly to be preferred to acute ligature because it gives any vessels present an opportunity to adjust to their new role in support of the heart.[55, 56]

Tests of revascularization based on backflow do not seem to be valuable with repetition because of their marked variation in the same dog at the same time.

Coronary arteriograms are easy to do using the technique described. Perhaps they could be done in the human to further clarify the sites of narrowing or obstruction in the coronary arteries as a preparation for surgical intervention. They certainly should be used in any study of this type to check on the occlusion of the coronary arteries produced while the animal is still living.

CONCLUSION

1. Cardiojejunopexy produces vascular communications between the intestine and the heart which are arteriolar or larger in size and do not show any tendency to close in up to twelve months.

2. When cardiojejunopexy dogs are compared with control dogs and with dogs with other types of revascularization by staged occlusion of the anterior descending and/or circumflex coronary arteries, a marked protection against death and infarction is demonstrated in the cardiojejunopexy dogs.

3. The staged occlusion of the coronary arteries with Goldblatt clamps has been a very effective method of producing partial and complete arterial occlusion.

4. Arteriograms offer an excellent method of determining the occlusion of a coronary artery. Coronary arteriograms could be valuable in the human in ascertaining the location and extent of coronary artery occlusion.

5. Fourteen cardiojejunopexy dogs have been produced with essentially all coronary artery supply occluded except the septal.

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Notice

Because of the large number of original communications awaiting publication in SURGERY, case reports are no longer being accepted.

—THE EDITORS.

Erratum

In the article entitled "A Technique of Abdominal Aortography and Femoral Arteriography" by Dr. Charles V. Menendez and Dr. Robert R. Linton, which appeared in the October issue of the JOURNAL, pages 718-736, the aortograms labeled Figs. 3 and 8 should be transposed. The illustration now appearing above the legend for Fig. 3 on page 723 should be placed above the legend for Fig. 8 on page 726. The normal aortogram, which now appears on page 726, should be transposed to page 723 and labeled Fig. 3.

Editorials

Marguerite Stadelhofer

On September 1, 1956, SURGERY lost a real friend by the death of Marguerite Stadelhofer, who at the time of the inception of SURGERY was Production Editor and subsequently Managing Editor of The C. V. Mosby Company. Had it not been for Miss Stadelhofer's vision, tremendous editorial experience, and determination, SURGERY would not be the journal it is today.

Marguerite Stadelhofer was born on September 30, 1895. She started employment at The Mosby Company in 1916 at the age of twenty as secretary and assistant to Mr. Paul Knabe, who was in charge of all the editorial work for the Company. At the time Miss Stadelhofer joined The Mosby Company, they published only two journals, but the number rapidly increased and Miss Stadelhofer was designated as Director of the Editorial Department. Probably no one person has been responsible for the inauguration and establishment of so many excellent journals as Miss Stadelhofer. She remained extremely active in the Company until about a year before her death. Even after she was taken ill, she returned to her duties and did a great deal of work. In January, 1954, Miss Stadelhofer had a radical mastectomy from which she recovered very quickly and resumed her full activities. However, in the summer of 1955, she began to have severe pain in her back but continued to work until October, when she was hospitalized, and for three months she underwent extensive x-ray and other therapy. During the period of her hospitalization, she directed the work of her department and even returned to her office in March and April, 1956, but finally had to discontinue all work because of the severe pain.

Marguerite Stadelhofer was a soldier to the very end. She was tireless in her endeavor and was undaunted by any obstacle. She lived an extremely full, active, and useful life and because of her efforts, medicine today is better than it would have been otherwise. Miss Stadelhofer had a large number of extremely devoted friends and her passing is indeed a great loss not only to those of us who knew her so well but also to medicine generally.

—*Alton Ochsner.*

Is the Treatment of Benign Thyroid Disease With Radioactive Iodine Without Danger?

With the availability of radioactive iodine, which is selectively taken up by the thyroid, its use in thyrotoxicosis was heralded as a great advance, because this form of therapy presumably could be used without the dangers

usually associated with an operative procedure and without the complications which occasionally occur following thyroidectomy. Obviously, if an equally good result can be obtained by a nonoperative form of therapy without any additional hazard, this method of therapy should be chosen. Although there is still considerable enthusiasm, particularly on the part of internists, concerning the use of radioactive iodine in the treatment of all diffuse hyperplastic thyroid glands, it is probably desirable to evaluate its results and possible complications. Unquestionably hyperplasia of the thyroid gland can be readily controlled by the use of radioactive iodine as effectively as by surgical methods. However, an obvious disadvantage of the use of radioactive iodine is that it is not easy to determine the exact amount required, and there is a possibility of producing too much destruction of the thyroid gland, with resultant hypothyroidism. Although hypothyroidism occasionally follows thyroidectomy, it is relatively easily prevented, because the surgeon can quite accurately determine the amount of gland which should be removed. Hypothyroidism in itself, however, is not too bad, because substitution therapy is relatively simple. It appears, therefore, that treatment of hyperplastic disease of the thyroid with radioactive iodine is an extremely valuable method of therapy and, if there are no other disadvantages from its use, it possibly might be preferred to other methods. However, an ionizing agent such as I^{131} may produce changes which will subsequently produce neoplasms. In 1950, Duffy and Fitzgerald[2] reported that among 28 patients, 18 years of age or younger, with cancer of the thyroid, observed at the Memorial Hospital, 10 had had previous irradiation of the thymus between the fourth and sixteenth months of life. Because of the possible causal relationship between irradiation of thymic enlargements in infancy and childhood and the development of neoplastic diseases subsequently, Simpson, Hempleman, and Fuller[3] studied 1,722 cases of thymic enlargement treated with x-ray. Eighty-one per cent of the entire group, or 1,400 patients, were followed, in addition to 1,795 untreated siblings. Sixty-seven of the treated children and 56 of the untreated children had died. Of the children who had received irradiation, 17, and possibly 19, children developed some form of cancer, 9 of whom died. Of the 1,795 in the control group in which no irradiation was used, four had cancer and one other had removal of a malignant tumor. Of the 17 treated cases which developed cancer, 7 had leukemia and 6 had carcinoma of the thyroid. An additional 9 children had thyroid adenomas. The study by Simpson and his co-workers showed that the expected and observed rates for neoplasia were as follows: The expected incidence of all cancers in both the irradiated and nonirradiated groups was 2.6 per cent, whereas the observed incidence in the former was 17 per cent, and possibly 19 per cent, and in the latter was 5 per cent. The expected incidence of leukemia in both groups was 0.6 per cent, whereas the observed incidence was 7 per cent, and possibly 8 per cent, in the irradiated group and none in the nonirradiated group. The expected incidence of thyroid cancer in both groups was 0.08 per cent, whereas the observed incidence was 6 per cent in the irradiated group and none in the nonirradiated group. These findings are particularly significant because the irradiation dosages were small.

Clark[1] observed 13 cases of children and adolescents within a period of six years with carcinoma of the thyroid, all of whom had had previous irradiation treatment. Three of these cases had irradiation of the chest for enlarged thymus, 3 had irradiation of the neck for cervical adenitis, 5 had irradiation to the head and neck for enlarged tonsils and adenoids, one had irradiation to the face and anterior chest for sinusitis and peribronchitis, and one had irradiation to the anterior upper chest for pertussis. In addition to these, there were two cases which he had not observed, but which he knew of by correspondence. One had received x-ray in early childhood for a chronic cough, the other had irradiation to the thymus in infancy. The interval from the irradiation to the date of the diagnosis of carcinoma of the thyroid varied from 3 to 10 years, with an average of 6.9 years. In 11 of the 13 cases, the dosage was small, 200 r, and in none of the cases did it exceed 725 r.

These statistics indicate that irradiation in relatively small doses, from 200 to 600 r, is dangerous as regards the development of subsequent malignant lesions. Although it is only recently that the danger from irradiation of the thymus has been appreciated, which is understandable because it is well known that irradiation damage does not become evident until many years have elapsed. it is likely that in the future many patients who have been given radioactive iodine therapeutically may develop complications. The dosages required are very much in excess of those which have been used in the treatment of thymic hyperplasia, and it is not beyond reason that one might expect carcinogenesis to occur within a much shorter period of time, and that, instead of an average of 6.9 years as observed in Clark's cases,[1] the length of time may be considerably shorter. It is, therefore, questionable whether radioactive iodine is ever justified in the treatment of benign thyroid conditions except in the patient in whom other forms of therapy are contraindicated or in the individual whose life expectancy is so short that the possible carcinogenic effect of the radioactive material may not occur. Does not the physician who undertakes the treatment of benign hyperplastic disease of the thyroid with I^{131} assume a responsibility which possibly is not justified?

—*Alton Ochsner.*

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Appraisal of Progress in Surgical Therapy

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THE EMERGENCE OF STANDARDIZATION IN THE TREATMENT OF THYROID CANCER

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THERE exists today a considerable difference of opinion in the management of tumors of the thyroid. Regardless of how bizarre the reader's own ideas may be concerning this subject, it is safe to say that he would have no trouble finding some author who has supported his ideas with a written thesis. Even the most sincere and astute physician finds it difficult to wade through this bewildering mass of information and emerge with a satisfactory set of principles to guide him in the numerous variations of this problem that are encountered.

Yet despite this conflicting information, all has not been entirely in vain. As one backs off and looks at the total picture, the evolution of certain principles upon which there is now reasonable agreement can be traced. Furthermore, newer information is now available that promises to help resolve some of the persistent controversial aspects. We believe that the next decade will see more common agreement on these principles and that this will lead to greater standardization of treatment. This paper will review the aspects of the problem we believe to be now reasonably settled and call attention to information which we hope will alleviate the despair that serious thinkers confronted with this problem encounter in their effort "to do the right thing."

FACTORS ADVERSELY AFFECTING PROPER EVALUATION OF THYROID TUMORS

The Natural History of Thyroid Cancer.—No single factor has made this problem more difficult than the inherent capricious behavior of thyroid cancer. As in other tumors, one finds thyroid cancers aggressive enough to kill the patient within less than a year despite the most valiant efforts at control. On the other end of the spectrum is the patient in whom the disease remains localized to the neck for accommodatingly long periods of time. There are others who are going about their daily activities despite radiographic evidence of

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bone destroying lesions or pulmonary metastases and in whom this known situation has existed for as long as ten to fifteen years. The disturbing thing is not that this variation in behavior exists, but that it is encountered so frequently. These variations in the natural history make the five-year-cure yardstick of limited use and render statistical evaluation of any specific mode of therapy most complex. For this reason, perhaps the soundest way to look at this problem is in the light of time-tested principles of cancer treatment that seem to have provided the basis for successful results achieved in the treatment of cancer elsewhere within the human body.

Pathology.—Cataloguing of tumor patterns began with Virchow, and the circulation of these histologic images eventually culminated in the acquisition of sufficient experience for pathologists to state after microscopic examination that a given tumor was "benign" or "malignant." However, one only has to reflect on the significance of the term "benign metastasizing struma" to appreciate the confusion that has existed in dealing with thyroid tumors.[2, 25] Few physicians with any experience have failed to remove a thyroid tumor which under the microscope appeared to be entirely benign but which ran a clinically malignant course. Agreement has also seemed hard to reach on the classification of thyroid cancers. For example, the differences in the end results of papillary thyroid cancer as reported by some authorities are so great that one wonders whether these authors could be talking about the same thing. It should also be appreciated that "pure" types do not always occur and that a mixture of papillary and follicular or alveolar elements is commonly encountered.

Although it must be admitted that the accuracy of the pathologist has not been as great in thyroid tumors as elsewhere, the gap is slowly being closed. Ackerman[1] states that he now feels capable of distinguishing a benign from a malignant thyroid tumor with a high degree of accuracy even with frozen section unless the picture is complicated by the additional factor of thyroid toxicity. Furthermore, it is his opinion that this degree of skill can be acquired by any pathologist provided he is granted the opportunity to gain sufficient experience with this mode of examination.

AREAS OF RELATIVELY COMMON AGREEMENT

Despite these difficulties, progress on agreement has been made. A survey of the literature will show that the majority of authorities are in agreement on the following eleven points:

1. *All Types of Thyroid Cancer Are Capable of Killing Patients.*—Superficially, it may appear unnecessary to make such a statement since any tumor diagnosed as "cancer" has by definition the capability of ultimately destroying the host. Nevertheless, papers have been written concerning the relatively innocuous nature of certain varieties of thyroid cancer, particularly papillary thyroid cancer,[9, 14, 15, 22, 33] and Crile[15] has even compared this cancer to a pimple. While all agree that there are variations in degrees of aggressiveness, it cannot be denied that even the so-called papillary thyroid cancer can destroy the patient. At Memorial Hospital where the treatment of this entity

has been described by some as being "aggressive" or even "radical," a survey showed that 21 per cent of these patients ultimately died of this form of the disease[27] if followed long enough. Some pimple!

2. *Benign Thyroid Tumors Cannot Be Distinguished From Malignant Ones on the Basis of Clinical Examination.*—There are instances where a clinical examination will almost certainly tell whether a lump in the thyroid is benign or malignant. For example, if paralysis of the larynx is present or there are enlarged lymph nodes in the neck associated with a lump in the thyroid, there would be little disagreement. Yet many times the sole sign is a mass in the thyroid gland, and the decision as to whether such a mass is benign or malignant is difficult enough even with the aid of the microscope. Most physicians recognize this and make no claims for being able to distinguish clinically the harmful from the harmless in such a setting. Despite the agreement of the majority on this point, some still[11, 13, 14] imply the possession of occult powers and educated finger tips that permit them to make this distinction on the basis of simple palpation or visualization. Even if we grant that there are such isolated, gifted individuals in our midst, it is certainly true that it is very difficult to teach and pass on these powers to other individuals.

3. *All Nodules in the Thyroid Deserve Exploration.*—Numerous analyses have been made of the incidence of carcinoma as it occurs in the otherwise asymptomatic nodule in the thyroid gland. Depending on which report one cares to accept, the incidence has been reported to range from 4 to 50 per cent.[3, 5, 8, 12, 29, 33, 34] The significant thing is that no such study has been made in which the conclusion has been reached that the incidence is 0 per cent. As one weighs the mortality of operations on the nontoxic gland (less than 1 per cent), the morbidity in the hospital (which averages four to five days), and the inconvenience of this procedure and balances it against the risks of adopting a "do-nothing policy" in from 4 to 50 per cent of individuals who are harboring a thyroid cancer, the conclusion is hard to escape that it is the physician who advises the watchful waiting and do-nothing policy who is radical and not the one who advises the patient to take definitive steps to get the matter settled. These statements do not require any alteration regardless of whether the thyroid masses are "single" or "multiple." Again, although some have stated that the incidence of cancer is higher[29, 39] in the multiple nodules and some have claimed the converse,[3, 5, 8, 12, 33] no study has shown a zero incidence in either case.

4. *Thyroid Cancer Can Occur at Any Age Beyond Infancy.*—In our own series the youngest patient with thyroid cancer was a 7-year-old white boy and the oldest was 80 years of age. Recognition of the fact that thyroid cancer can occur in children is now adequately documented.[18, 38, 44, 47] No conclusions can be based on the possible malignancy or benignity of a lump in the thyroid based on age alone.

5. *Thyroid Cancer Affects Both Sexes.*—The typical thyroid cancer patient is a female and usually in the young adult or middle-aged decades. Large

series show the ratio in females over males to be approximately 70 per cent to 30 per cent. For practical purposes, therefore, one must anticipate its occurrence in either sex.

6. *There Is no Safe Period After Which Thyroid Masses Are no Longer Capable of Becoming Malignant.*—This point is apt to be of more importance in dealing with patients than with physicians. One frequently hears a patient state that the mass in the thyroid has been present a long time, that it has remained unchanged, and that they therefore see no reason to do anything about it at the present time. We recently operated upon a patient who first noted a nodule in her thyroid at 18 years of age and, 35 years later, experienced a marked and rapid increase in size of the "goiter" with the appearance of nodules in the lateral part of the neck. The tumor proved to be a cancer and the patient was operated upon, but obviously with a considerably less chance of a good result than if the operation had been carried out at a time when the tumor was still benign. Tumors that have remained unchanged over long periods of time have a greater chance of being benign than those of more recent origin, but this is only a generality and not an absolute rule.

7. *Lateral Aberrant Thyroid Masses Are a Myth.*—Despite attractive embryologic explanations[4, 6, 10, 21, 32, 35] for the occurrence of thyroid tissue in the lateral portions of the neck in areas anatomically distinct from the thyroid gland itself, modern evidence supports the belief that such lumps are in reality metastases.[17, 20, 45, 46, 48] Even though a primary tumor in the thyroid gland may not be clinically obvious, the chances are that such exists. Interested pathologists who are willing to make detailed serial sections of the thyroid gland will find a primary tumor in every case.*

8. *Radioactive Iodine Has Never Cured a Case of Thyroid Cancer.*—Although radioactive iodine is a helpful palliative agent in approximately 15 to 20 per cent of all thyroid cancer cases,[19, 23, 24, 30, 43] there are no grounds at the present for claiming even a single cure with this method. It has been in common usage somewhat less than a decade. Considering the vagaries of thyroid cancer, it will be realized that any such claims for cure are premature. Its use as a diagnostic aid to distinguish a benign from a malignant mass is utterly worthless and only delays definitive settlement of the problem.

9. *Surgery Is the Most Effective Available Method of Treating Thyroid Cancer.*—There is universal agreement that surgery is the most efficacious method of attempting to eradicate thyroid cancer. As will be subsequently discussed, the controversies do not concern *whether* surgery should be used, but *how* it should be used.

10. *Presence of Toxicity Does Not Exclude the Possibility of Coexistent Cancer.*—The chances of cancer being present in a patient who also shows toxic metabolic disturbances are low but do exist. Associated toxicity reduces but does not totally exclude such a possibility.

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*In this connection the statement of Dr. Hayes Martin[39] to the effect that if lateral aberrant thyroid exists, it is curious that in the course of several thousand radical neck dissections for diseases other than those associated with thyroid cancer there was not a single instance in which a lateral aberrant thyroid was uncovered as an incidental asymptomatic finding is of interest.

11. *Radiation Therapy Is Only of Limited Value in Thyroid Cancer.*—Radiation usually has been advocated as an adjunct to surgical treatment and beneficial results have been claimed.[7, 8, 31] Others dispute its value.[10, 39] When applied, the most popular scheme is to direct the energy to the neck postoperatively with the hope of sterilizing residual cancer cells left in this area. To cover this possibility, the radiologist is forced to include in the field an area extending from the mandible to the clavicle and from the anterior midline to the trapezial borders. With fields this large, serious handicaps to effective treatment are imposed and most radiologists will admit that unless one is dealing with an extremely sensitive tumor (e.g., lymphoma) such efforts are of questionable value.

There is no evidence that thyroid cancer possesses this degree of sensitivity. Also, to the best of our knowledge, there does not exist any report of cases treated solely with x-ray, and when used with surgery its evaluation is difficult. As a palliative agent in relief of bone pain from metastasis its use seems valid, but its failure to eradicate recurrences growing into the trachea, larynx, and esophagus has been too discouragingly obvious even when the fields have been reduced and pinpointed to fit this objective. To fair-minded observers, therefore, there seems little reason to subject the patient to haphazard, routine "prophylactic" radiation therapy to the entire neck. If used at all, it appears wiser to restrict it until clinical evidence of disease has occurred, thus permitting the radiologist to use this tool "as a rifle and not as a shotgun."

CONTROVERSIAL POINTS CONCERNING CHOICE OF SURGICAL TREATMENT

As indicated, the controversies about the surgical treatment of thyroid cancer do not concern whether it should be employed, but exactly how much surgery should be carried out, and how this must be varied to meet different situations. A discussion of some of the more controversial aspects with suggested solutions follows.

Removing the Primary Thyroid Mass.—Differences concerning removal of nodules in the thyroid narrow down to those who advise "shelling out" the nodule[34] and those who advise wider methods of removal. The only reason for operating on a patient with an asymptomatic nodule in the thyroid gland is the fact that such a lesion is cancer now or may ultimately become so. Bearing this in mind, the operation should be planned to remove the suspected abnormal tissue with a rim of uninvolved tissue surrounding it in all planes. Sometimes the location of the nodule does not permit this. Nevertheless, this objective should remain foremost in the operator's mind. Most cases require lobectomy with exposure and dissection of the recurrent nerve as an inherent part of the operation. If the patient has a normal thyroid gland to begin with, the removal of one lobe does not cause any metabolic handicaps.

Subtotal vs. Total Thyroidectomy.—In removing a cancer in any location, the objective is not only to remove the cancerous tissue, but to include a margin of normal tissue in all planes to insure that the cut margins of the specimen have been placed beyond the point where microscopic spread of tumor can be demon-

strated. At present it is our feeling that in the majority of circumstances this can be accomplished without removing the entire thyroid gland. The problem of multicentric origin of thyroid cancer does exist and one cannot deny that as long as any thyroid tissue is left such a possibility cannot be excluded.

Studies of MacDonald,[36] Ackerman,[1] and Frazell,[26] who have shown a particular interest in the problem of thyroid cancer, indicate that some modification in this line of thinking may ultimately be required. This is based on the fact that the tumors have been found to extend beyond the margins of excision in a respectable proportion of cases when the operations have been carried out by even the most capable of surgeons, as well as certain evidence of multicentric origin.

Our efforts, however, have been directed toward formulating policies that can be carried out with a high expectation of long-term salvage and at the same time not be handicapped by excessive morbidity. While it is true that the total thyroid gland can be removed and appropriate substitutions be made through the courtesy of pharmaceutical firms, such a regimen does have nuisance value and, unless it is of proved value, seems worth obviating.

The economic price of total thyroid removal is approximately 3 cents a day for artificial substitutes plus continued follow-up in some physician's office for regulation of required doses. These are surmountable obstacles and, if subsequent studies show that total thyroidectomy is preferable to lesser procedures, postoperative regimens can be worked out. Until such a time when the evidence in favor of total thyroidectomy gains a firmer footing we shall continue to consider it desirable to save at least a portion of normally functioning thyroid gland if this does not compromise total removal of tumor, with the hope that the patient can return to as regular a life as possible following the operation.

Does Neck Dissection Do an Efficient Job in Removal of Thyroid Cancer?—Surgery cures cancer only when the neoplasm is limited to the primary site or to the primary site plus the regional lymph nodes. Once spread has occurred by the blood stream or gone beyond these primary echelons, only palliation can be expected. The feeling is sometimes expressed that neck dissection is only of limited value in thyroid cancer since metastases occur to the mediastinal and other lymph nodes which are not removed in the ordinary dissection.

Is there reason to expect that neck dissection is effective in accomplishing total removal of cancerous tissue? The recent work of Frazell and Foote[28] should help in evaluation of this point. In this study a detailed analysis was made of 182 specimens removed from the necks of patients operated upon with papillary thyroid cancer. The patients were divided into two groups: (a) those in whom there *was clinical evidence of cervical metastases* and (b) those in whom there *was no clinical evidence of metastases.* If microscopic evidence of cervical metastases was present, it was plotted according to the level of lymph node involvement (Fig. 1). The first thing to come out of the analysis was that even though there was no clinical evidence of metastases, microscopic study showed them to be present in 61 per cent of the specimens. Also, in the patients receiving the neck dissection in the absence of clinical evidence of

TABLE I. PAPILLARY THYROID CANCER. NODE INVOLVEMENT BY LEVELS

NODE LEVEL	CLINICALLY POSITIVE PATIENTS (115) (%)	CLINICALLY NEGATIVE PATIENTS (67) (%)
Submaxillary	9.7	1.5
Upper jugular	61	19
Mid-jugular	76	30
Low jugular	76	33
Spinal accessory	36	6
Juxtathyroid	32	13
Mediastinal	6	0

Histologically positive cervical nodes were found in 61.2 per cent of patients in whom there was no clinical evidence of metastases present. (From Frazell and Foote, Cancer 8: 1164, 1955.)

metastases, the metastatic deposits were confined to the node levels normally adequately removed in this operation. The nodes at the peripheral margins of the dissection were only rarely positive. (Table I.) Conversely, in those with clinical evidence of metastases, the nodes at the periphery of the specimen were positive in a significantly higher percentage. When considered from the point of view of multiplicity of node groups involved, the disease was confined to only one or two levels in about 80 per cent of the patients receiving the "elective" or "prophylactic" operation. In contrast, the disease was similarly confined in only 36 per cent in those patients with clinical evidence of disease.

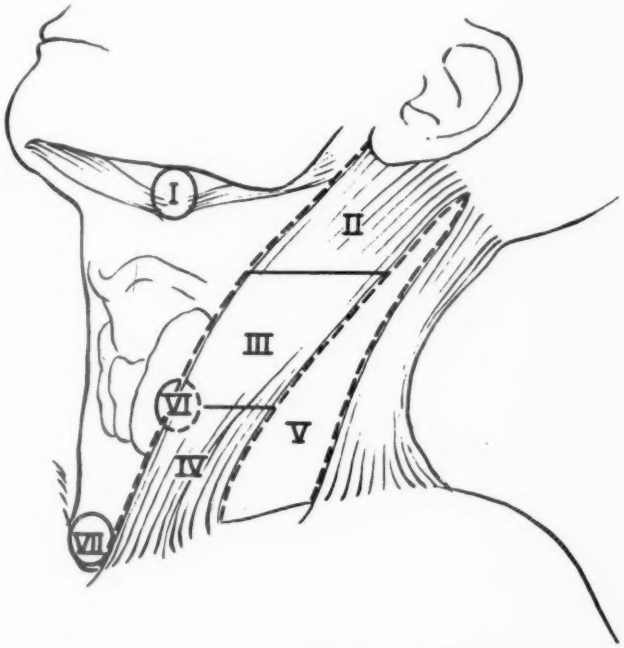

Fig. 1.—Node-bearing areas removed by radical neck dissection for thyroid cancer. Level I, submaxillary; level II, upper jugular; level III, middle jugular; level IV, lower jugular; level V, accessory chain; level VI, juxtathyroid; level VII, anterior mediastinal nodes. (From Frazell and Foote, Cancer 8: 1164, 1955.)

It appears therefore, that neck dissection, if carried out early, may have a good chance of completely removing all local cancerous tissue. One might still question its employment if it were attended with a high mortality and

morbidity, but in the proper hands the mortality rate from neck dissection should be about 1 per cent. The patient spends an average of 8 days in the hospital and recovers with little or no functional disturbance particularly if the spinal accessory nerve is preserved. The operation, therefore, appears to meet all necessary qualifications from the point of view of promising reasonable salvage, mortality and morbidity and cannot be ruled out on these grounds.

Prophylactic vs. Therapeutic Neck Dissections.—Joint attack on the primary tumor in the thyroid and the metastatic nodes is not questioned whenever there is clinical evidence of involvement of the cervical lymph nodes. Only recently, however, has the concept of treating the primary thyroid cancer and at the same time doing a neck dissection even in the absence of clinical evidence of cervical metastases gained any real support. Experience in the treatment of squamous carcinoma of the head and the neck has shown that when a neck dissection is done on a "fresh" neck, the results are considerably better than if this operation is done on a neck which has been previously entered and the concept is gaining ground of attempting to treat the primary tumor and the metastatic nodes at one sitting *whenever the removal of the primary tumor itself dictates that the neck be entered.*

Surgeons believe their operations to be more effective when a limited amount of cancerous tissue is removed than when they are called upon to remove excessive amounts. The classical cancer operations such as radical mastectomy, abdominoperineal resection, and combined neck and jaw resection are all planned to remove the primary tumor and the regional lymph nodes at one sitting. Thyroid cancer has the same predisposition to metastasize by way of the lymphatic stream as these tumors. Anatomically, it is not always possible to operate in accord with these axioms (e.g., malignant melanoma on foot or leg with groin metastases), but nothing has developed to change the fact that this should be the desired objective of cancer operations. In many cancers of the thyroid there is no anatomic barrier to hinder the application of the above principles.

If we accept these principles as being sound when applied to cancer of the breast, rectum, or gum, why should we make an exception in the case of the thyroid? One cannot help but wonder, therefore, whether one should not approach nodules in the thyroid in the same manner as a lump in the female breast, where it is agreed that once the diagnosis of breast cancer is established a complete radical mastectomy should be carried out even though there may be no clinical evidence of axillary metastases.

In view of all this, it appears to us that the proper way to treat a nodule in the thyroid is to make the usual collar incision, expose the thyroid gland, and remove the suspected nodule with a wide margin. This specimen should then be sent to the laboratory and examined by a frozen section. If a diagnosis of carcinoma is returned, the incision should then be converted into one suitable to accommodate a radical neck dissection, and the neck dissection should be done at this sitting.

Resistance exists in some quarters to an attempt to make a diagnosis of a thyroid cancer on the basis of a frozen section alone. This is a surmountable objection. At least part of the fault lies with the fact that pathologists have never been asked by enough surgeons to make such an examination and, therefore, have not attained sufficient experience to warrant confidence in their evaluation. The pathologists at Memorial Hospital and Dr. Lauren Ackerman of St. Louis have cooperated in such an attempt and have been able to establish a diagnosis of cancer when it exists in better than 95 per cent of the cases by means of a frozen section when requested to do so. What few errors have been made have consisted of calling a tumor benign when later paraffin studies showed it to be malignant. As stated earlier, it is the association of toxicity that provides the greatest difficulty to the establishment of diagnosis by such means, but this is a rare handicap and we believe that if all surgeons, instead of an isolated few, requested the pathologists to examine thyroid nodules with a frozen section, eventually other pathologists would gain the same skill and confidence that Ackerman, Stewart, and Foote, and others have attained.

If the diagnosis is returned as benign, the simple collar incision is then closed in the routine fashion and nothing further is done. If no attempt is made to obtain a diagnosis at the time of the first operation and the surgeon is forced to confront the family two or three days later with the fact that the nodule was cancerous, he is immediately placed in a state of great indecision. He must now decide whether to do nothing further, whether to reoperate and attempt to gain a wider margin around the tumor than he removed with the belief that it was probably benign, whether a neck dissection should be done now, whether it should be deferred until clinical evidence of disease appears, whether postoperative x-ray should be given, whether radioactive iodine should be given, and so forth. The uncertainties concerning proper choice of treatment felt by the surgeon are transferred to the patient and family and cannot help but breed a certain amount of uneasiness.

When a family is confronted with the diagnosis of cancer, the one thing that they want to feel above all else is that everything humanly possible has been done to offer the patient the best chance of cure. Therefore, if the surgeon has to make such a diagnosis but can then follow it with statements to the effect that, although this is true, everything has now been done to assure this individual that she has heard the last of the problem, his position is stronger. This leads to greater satisfaction on the part of both the physician and his patient.

While we believe that the treatment of thyroid cancer should be carried out in accord with the above principles, it must be admitted that there still occur situations where these guides for treatment still do not provide a wholly satisfactory solution. Under such circumstances one is forced to compromise and deal with the situation the way it exists, and not the way he would like it to exist. When one tabulates the incidence of these situations, the only encouraging thing that can be said is that while they do occur disturbingly frequently,

nevertheless they comprise the minority, and operating in accord with the previously described principles will be of help in dealing with the majority of patients.

The Midline Nodule.—The problem of the midline thyroid nodule is a good example. Aside from stating that the nodule should be removed with a wide rim of uninvolved tissue, it is difficult to advise what to do next in the absence of any clinical involvement of any cervical lymph nodes. For, if one is dedicated to the principle of performing "prophylactic" neck dissections in the presence of thyroid cancer, which side should the neck dissection be done on in such a setting? There is obviously no more reason to expect trouble on the right than on the left side, and, to be consistent, one is forced to the somewhat untenable position of performing a bilateral radical neck dissection at one sitting. Although this is feasible in certain settings,[40, 41] no one denies that it is a formidable procedure and in our opinion is seldom justified. Under such circumstances, therefore, we believe that the wisest thing to do is to remove the primary tumor only and defer any neck dissection until clinical evidence of disease shows up.

The Primary Tumor Mass Crossing the Midline, With no Clinical Evidence of Metastases.—Here again, the surgeon is faced with an unsatisfactory situation. It cannot be denied that bilateral spread may have taken place and yet bilateral neck dissection seems unduly aggressive treatment. Playing the odds, it seems reasonable to expect that, with a tumor this large, metastases are more likely to exist on the side of the neck comparable to the side of thyroid gland which is more extensively involved with cancer. Faced with such a situation we carry out the neck dissection on the side corresponding to the side showing the greatest involvement at the primary site and defer any further surgery to the remaining side of the neck until clinical evidence of disease shows up.

The Problem of Bilateral Cervical Metastases.—It may be questioned whether it is advisable to carry out extensive surgery on patients showing such an advanced degree of involvement. Examination of the clinical courses of such individuals does *not* support such a position. We believe that such individuals should be treated with bilateral neck dissection as staged procedures. This position is supported first of all by a significant number of long-term survivals following this treatment (Fig. 2). A second aspect of the problem concerns the fact that many individuals so treated have never again developed any trouble in the neck although death from distant metastases has taken place. Even so, considered from a palliative point of view, we believe that such individuals have been benefited by the operation since their mode of exodus from distant metastases has been considerably easier to deal with when compared with those whose life is slowly throttled away due to invasion of the trachea, esophagus, etc. The safety of staged bilateral neck dissections is attested to by a series of 66 individuals so treated, with a mortality of 0 per cent.[40] In most cases it is possible to preserve the jugular vein on the side of less involvement and to decrease the morbidity in so doing.

Primary Tumor Already Removed, Diagnosis of Cancer Established, Patient Referred for Further Treatment.—This situation constitutes one of the most unsatisfactory problems encountered. Such individuals show up at the clinic with a recent collar incision, and except for the information that a diagnosis of cancer is established, the consultant has little to go on. Specifically, he has no first-hand information on the precise location of the primary tumor, its size, and whether or not complete local removal has been carried out. If he elects to reoperate, he is forced to do so in a field already entered and scarred from the previous operation, making satisfactory dissection questionable.

Fig. 2.—Five years ago this 17-year-old white girl presented herself with bilateral cervical metastases and a primary thyroid cancer of mixed papillary and alveolar type. She was treated with a staged bilateral neck dissection and total thyroidectomy. She is still symptom-free. Staged bilateral neck dissection is a safe procedure, produces respectable salvage, and in many cases prevents the patient from dying from invasion of trachea, esophagus, etc. It should be considered in all varieties of thyroid cancer except giant-cell carcinoma.

If there is clinical evidence of metastases in the neck, we believe that the patient should be reoperated upon in such a way as to attempt a wider dissection of the primary tumor site together with the cervical lymph nodes. In the absence of clinical evidence of cervical node metastases, we have been forced to be satisfied with simply waiting and observing the patient until this disease develops. The number of such cases would be decreased if the first surgeon operating accepts total responsibility for the treatment and is morally and professionally qualified to deal with any situation that may be encountered.

Surgery in the More Anaplastic Types.—The prognosis in thyroid cancer is determined not only by the extent of the disease when definitive treatment is

instituted, but upon the histologic type of tumor. Papillary adenocarcinoma comprises about 50 per cent of all thyroid cancers and carries the best prognosis. Though less successful, efforts at surgical control appear justified in follicular (and alveolar) carcinoma, "solid" adenocarcinoma, and Hürthle cell carcinoma.[14]

To the contrary, when one encounters a giant-cell carcinoma of the thyroid, no treatment alters in any way the ultimate fatal outcome. Fortunately, these tumors comprise only about 13 per cent of the total group.[14] Once such a diagnosis is established, there seems to be no point in attempting surgical treatment since not a single cure of this variety has ever been achieved.

SUMMARY AND CONCLUSION

The complexities of the problem of thyroid cancer have been reviewed. Despite the differences of opinion on many aspects, a survey of the literature shows that agreement by most authorities has been reached on many points. Eleven of these are outlined. Evidence in the literature and our own personal experience supports the belief that surgery is the most efficacious method of treating thyroid cancer. The operation of radical neck dissection is a procedure attended with a reasonable morbidity and mortality and we believe it to be efficacious in accomplishing total removal of cancerous tissue. Its efficacy is dependent among other things on the stage of disease when it is employed, there being reason to expect the salvage rate to be higher in cases of limited involvement, and vice versa.

The performance of a neck dissection in the absence of clinical evidence of cervical metastasis is in accord with time-tested principles of cancer surgery as applied in other parts of the body and can be used in the majority of thyroid cancer situations. To us this appears much more satisfactory than some less aggressive treatment executed with the hope that the patient is one of the fortunate individuals afflicted with a biologically favorable unaggressive cancer and that this cancer is not going to hurt anyone anyway and no one needs to take very positive steps in its treatment.

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In Memoriam

VILRAY PAPIN BLAIR

1871-1955

THERE have been many well-deserved honors conferred on Vilray Blair. Splendid tributes to his professional achievements and personality have been published. These are so comprehensive that nothing is left to add to them. A list of the publications is found below.

Perhaps Blair's greatest role, that of a teacher, has been either overlooked or, at least with a few exceptions, not emphasized. His teaching began in 1894, the year following his graduation from the Washington University Medical School. He was made Lecturer on Descriptive Anatomy for both his Alma Mater and the affiliated Dental School. The title is misleading because the teaching was done almost exclusively by human dissection in a well-supplied and excellently equipped anatomical laboratory. Under various titles, including that of Associate Professor in 1905, he continued teaching practical anatomy in both schools for approximately 18 years (on a part-time basis) while at the same time engaged in the practice of general surgery.

Blair's innate artistic sense led him to develop a method of teaching anatomy by having students model parts under study in clay. It is possible that this idea appeared to be a practical one through close contact with the Dental School and the methods there used in making prostheses. That contact doubtless stimulated him to acquire the profound knowledge he had of the embryology, development, anatomy, physiology, pathology, congenital defects, and trauma of what may be termed the nasal-facial-oral dental-pharyngeal-laryngeal complex and the intricate relationships involved. To this should be added breathing and the esthetics of facial expressions, articulation, and vocal quality. This does not mean that Blair was less informed on other simpler anatomical divisions.

In 1895, Washington University Medical and Dental Schools chose Robert J. Terry, M.D., to head the Departments of Anatomy. Up to that time anatomical teaching had been done by surgeons. Dissecting laboratory teaching was carried on with the help of part-time demonstrators, chiefly surgeons, one of whom was Blair.

From a lifetime of intimate, devoted friendship and 18 years' association in teaching, Robert J. Terry, Professor Emeritus of Anatomy, writes as follows: "In the foreground of a picture of Vilray Blair's traits is a super-dynamo of power in mind and hand. His inventiveness was a resource applied not only in the field of plastic surgery but in mechanics, architecture, methods of teaching and in many other directions. His part in the organization of the Schools

of Oral and Plastic Surgery, a necessary and essential plan to recruit and train surgeons for service in World War I, was a wonderful idea proposed, with splendid results achieved. Those who saw the friendly informal surgeon away from the operating room would never guess of Blair's precision in action. Inventiveness, practicality, and dexterity, native traits, combined with a profound knowledge of anatomy were the elements revealed in his successful treatment of the patient and basic in his fine contribution to medicine." To this can be added the ability critically to examine, evaluate, and depart from the accepted and orthodox if so doing promised the achievement of the end in view. In surgery the welfare of the patient was always Blair's guiding thought; one may even say his sacred principle.

Though occasionally substituting as a lecturer on a clinical surgical subject, Blair was not identified with the Department of Surgery until his appointment as one of the chiefs of the outpatient Surgical Clinics of the Washington University Hospital in 1908. He was made Clinical Professor of Surgery in 1911 and Associate Professor of Surgery and Professor of Oral Surgery in the Dental School the following year. The title of Associate Professor continued until retirement in 1941 when he became Emeritus but remained active in the practice of surgery. When the Barnes Hospital was opened in 1915, the Washington University Hospital was closed. Blair's staff appointment was transferred to the former.

In the exacting task of teaching anatomy to medical and dental students, to his profound knowledge of the subject and the clinical implications involved, Blair brought infinite patience, geniality, and a fine sense of humor. These qualities were equally carried over into surgical instruction of students and, later, house officers. They were so impressive that whatever was being taught would be remembered. To the young physician or surgeon seeking advice, Blair was as generous of his time as he was wise of counsel, and as far as lay in his power endeavored to further their interests.

The foregoing qualities were aptly and fully characterized by the late Barney Brooks in the following quotation: "I can say without any reservation that I have learned more from Vilray Blair than from any other man officially, so to speak, not my teacher. I remember and frequently quote remarks he made years ago. He has always had the happy faculty of saying things in a manner entertaining and witty and therefore easy and pleasant to remember. I have found not infrequently that a remark of his contained a depth of meaning which I only fully appreciated years afterward."

As a practitioner of general surgery which ranged from operations for brain tumor and trigeminal neuralgia to exstrophy of the bladder, Blair's daring, imagination, and artistic sense resulted in the most difficult cases being referred to him. Two such are unforgettable. A young physician had extreme prognathism, and an adolescent girl had a receding chin; both verged on psychological catastrophe. Blair resected the mandible and retreated the chin in the first case and advanced it in the second case. The physician became a successful practitioner of more than average good looks.

It is fitting at this point to quote Evarts Graham who in his inimitable style used these words on presentation of Honorary Degree of Doctor of

Science by Washington University: "Sculptor not in clay or marble, but in living flesh. Magician in restoring the maimed to normal and transforming the ugly to the beautiful."

Not only could Blair foresee the result of a plastic or corrective procedure, but he had an astonishing capacity to evaluate what may be called the vital force of a patient as a whole or of his tissue as a part. No less accurate was his ability to separate sheer vanity on the one hand and psychic need on the other when "cosmetic surgery" was so much to the fore. Needless to say, he had no part in the former.

In medicine Blair, the teacher, has had a lasting impact and influence on almost numberless medical and dental students, house officers, and colleagues. Contact with him was of incalculable value to me as to many another. This began in the dissecting hall in 1901 in the course of an attempt to dissect the palm of a wasted, unpromising cadaver. Since I was completely baffled, Blair took over, quickly exposed the thenar nerve, palmar arch, and tendon sheaths while emphasizing their importance in the surgical treatment of infection of the palmar aspect of the hand. This experience after many years still remains clear. Equally so was a lecture (in the third year) on the Hodgen splint, its theory, origin (treatment of gunshot fractures of the femur in the Civil War), indications, application, and efficiency.

When the writer was an intern in the St. Louis City Hospital, there was the opportunity to see the dreadful cancers of the face and mouth, products of ignorance, poverty, neglect, and medical conservatism of that period. Blair was occasionally called in for them. There was learned the clinical importance of differentiation between lateral extension and remote metastasis as a guide for treatment, also that radical measures, no matter how mutilating, were justifiable because they would make life less intolerable. This was especially so in the case of the mouth and tongue. Further, much could be done to improve resulting surgical defects. Somewhat later the dire possibilities inherent in infections of the lip, nose, and face were learned. One such example was a case of fulminant osteomyelitis involving all the bones of the face lying below the base of the skull except the mandible, in which Blair was called into consultation by the late Greenfield Sluder. The imprint of these recollections is not to be traced to their occurrence in the impressionable years for there was equal impact in maturity.

From 1898 to 1950 Blair published 6 texts and 172 articles. Of the latter, 150 are on oral and plastic subjects, many written in collaboration with his gifted younger associates. Blair had unerring capacity to detect latent talent in young surgeons and develop them into brilliant successors in his field.

In the trench warfare of World War I, wounds of the head and face exceeded in number and severity those of any previous conflict. To Vilray Blair was given the task of organizing the methods of caring for wounds of the face and jaws. His accomplishments were monumental. They have been well described and are referred to above. It is a singular tribute to Blair that in World War II associates and former associates played an important and brilliant part in the care of plastic casualties. To wounds were added a tragic number of burns suffered by aviators. James Barrett Brown headed the Plas-

tic and Reconstructive Service of the Army with headquarters at Valley Forge General Hospital. With him were Bradford Cannon, Eugene Bricker, and Carl Lischer, the last two, though never a part of Blair's group, were resident surgeons in the Barnes Hospital fully trained in plastic and reconstructive surgery. In the Navy, William G. Hamm, after a mission as medical officer to North Africa (preliminary to its invasion), returned to take charge of the Plastic Surgery Service at St. Albans Naval Hospital on Long Island. He was later made chief of the entire surgical service and was discharged with the rank of Rear Admiral.

An early example of Blair's comprehensive interests lies in the fact that he worked with Dr. W. W. Graves who had a static x-ray generator, one of the earliest if not the first in St. Louis. Graves gave this up in 1898 because of radiation injuries to his hands. Throughout his long life Blair, from time to time, had occasion to treat Graves' injuries, doubtless forestalling the development of radiation carcinoma. Graves was the forerunner of an ever-enlarging number of professional victims of radiation. In their management there was no temporizing, cautery, coagulation, and the like, but complete excision and grafting.

In this connection it is not too great a digression to record that with the late Ellis Fischel Blair began early the use of radium and radon implantation in the treatment of carcinoma. He had indeed a full grasp of the fundamentals of both radium and roentgen radiation, their capabilities, and limitations. In roentgenology Blair was a master of method and interpretation in examination of the jaws and the temporomandibular joint. Equally great was his grasp of the principles of roentgen therapy, its possibilities, and limitations. More than once it happened that following Blair's advice, roentgen treatment was given to patients seemingly beyond hope, only to have them return years later free of disease.

When one worked in close cooperation with Blair and his associates, there was always the comforting assurance that should disaster attend x-ray treatment it could be remedied successfully. This permitted a thoroughness of administration sometimes condemned as reckless, though no untoward result occurred.

To have been taught by Vilray Blair, associated with him professionally for most of a lifetime, and honored with his friendship gives rise to a profound sense of affection for his memory.

—Sherwood Moore

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Calendar of Surgical Meetings

1956

AMERICAN MEDICAL ASSOCIATION. *Clinical Session,* Nov. 27-30, 1956, Civic Auditorium, Seattle, Wash. Secretary, Council on Scientific Assembly, A. M. A., 535 N. Dearborn St., Chicago 10, Ill.

LATIN AMERICAN CHAPTER OF INTERNATIONAL SOCIETY OF ANGIOLOGY. *Third Meeting,* Nov. 8-11, 1956, Havana, Cuba. President, Armando Núñez Núñez, Calle 25 No. 510, Vedado, Havana, Cuba.

SOUTHERN SURGICAL ASSOCIATION. *Annual Meeting,* Dec. 4-6, 1956, the Boca Raton Club and Hotel, Boca Raton, Fla. Secretary, George G. Finney, M.D., 2947 St. Paul St., Baltimore, Md.

1957

THE AMERICAN ASSOCIATION FOR THORACIC SURGERY. *Annual Meeting,* May 4, 6, and 7, 1957, The Palmer House, Chicago, Ill. Deadline for papers, Dec. 15, 1956. Secretary, H. T. Langston, M.D., 1919 West Taylor St., Chicago 12, Ill.

AMERICAN ASSOCIATION OF GENITO-URINARY SURGEONS. *Annual Meeting,* May 1, 2, and 3, 1957, The Homestead, Hot Springs, Va. Secretary, John A. Taylor, M.D., 2 East 54th Street, New York 22, N. Y.

AMERICAN ASSOCIATION FOR THE SURGERY OF TRAUMA. *Annual Meeting,* Oct. 31, Nov. 1 and 2, 1957, The Homestead, Hot Springs, Va. Deadline for papers, Aug. 1, 1957. Secretary, James K. Stack, 700 N. Michigan Ave., Chicago 11, Ill.

AMERICAN COLLEGE OF SURGEONS. *Sectional Meetings,* 1957: Jan. 16-18, Caribe Hilton, San Juan, Puerto Rico; Feb. 4-7, Hotels Jung and Roosevelt, New Orleans, La.; Feb. 28-March 2, The Olympic Hotel, Seattle, Wash.; March 18-20, The Sheraton-Park Hotel, Washington, D. C.; March 25-27, The Royal York, Toronto, Ontario. *Clinical Congress,* Oct. 14-18, Convention Hall, Atlantic City, N. J. Secretary of the College, Michael L. Mason, 154 E. Erie St., Chicago 11, Ill.

AMERICAN COLLEGE OF SURGEONS. Southern California Chapter. *Annual Meeting,* Jan. 18, 19, and 20, 1957, Biltmore Hotel, Santa Barbara, Calif. Secretary-Treasurer, Max R. Gaspar, M.D., 211 Cherry Avenue, Long Beach 2, Calif.

AMERICAN GYNECOLOGICAL SOCIETY. *Annual Meeting,* May 27, 28, and 29, 1957, The Homestead, Hot Springs, Va. Secretary, Andrew A. Marchetti, M.D., Georgetown University Hospital, Washington 7, D. C.

AMERICAN MEDICAL ASSOCIATION. *Annual Meeting,* June 3-7, 1957, Coliseum, New York, N. Y. Deadline for papers, Dec. 15, 1956. *Clinical Meeting,* Dec. 3-6, 1957, Auditorium, Philadelphia, Pa. Deadline for papers, July 15, 1957. Secretary, American Medical Association, George F. Lull, M.D.; Secretary, Council on Scientific Assembly, Thomas G. Hull, M.D.; address of both, 535 North Dearborn Street, Chicago 10, Ill.

AMERICAN SURGICAL ASSOCIATION. *Annual Meeting,* May 8, 9, and 10, 1957, The Palmer House, Chicago, Ill. Secretary, R. K. Gilchrist, M.D., 59 East Madison Street, Chicago 3, Ill.

AMERICAN UROLOGICAL ASSOCIATION. *Annual Meeting,* May 6-9, 1957, William Penn Hotel, Pittsburgh, Pa. Deadline for papers, Jan. 1, 1957. Secretary, Samuel L. Raines, M.D., 188 S. Bellevue Blvd., Memphis, Tenn.

THE CENTRAL SURGICAL ASSOCIATION. *Annual Meeting,* Feb. 21-23, 1957, The Drake Hotel, Chicago, Ill. Deadline for papers, Oct. 15, 1956. Secretary, Charles D. Branch, M.D., 102 North St., Peoria, Ill.

NEW ENGLAND SURGICAL SOCIETY. *Annual Meeting,* Oct. 4 and 5, 1957, Mount Washington Hotel, Burton Woods, N. H. Deadline for papers, June 1, 1957. Secretary, Richard Warren, M.D., Peter Bent Brigham Hospital, 721 Huntington Avenue, Boston 15, Mass.

THE PACIFIC COAST SURGICAL ASSOCIATION. *Annual Meeting,* Feb. 4-6, 1957, El Mirador Hotel, Palm Springs, Calif. Secretary, Carleton Mathewson, Jr., M.D., Stanford University Hospital, San Francisco 15, Calif.

PAN-PACIFIC SURGICAL ASSOCIATION. *Annual Meeting,* Nov. 14-22, 1957, Honolulu, Hawaii. Director General, F. J. Pinkerton, M.D., Room 230, Young Building, Honolulu, Hawaii.

THE SOCIETY OF UNIVERSITY SURGEONS. *Annual Meeting,* Feb. 7-9, 1957. the Deshler-Hilton Hotel, Columbus, Ohio. Abstracts to be received by Dr. Ben Eiseman, Chairman, Committee on Publications, 4200 E. Ninth Ave., Denver 20, Colo., by Nov. 15, 1956. Secretary, James D. Hardy, M.D., Hospital of the University of Mississippi, Jackson, Miss.

THE SOCIETY FOR VASCULAR SURGERY. *Annual Meeting,* June 2, 1957, Hotel Biltmore, New York, N. Y. Secretary, Henry Swan, M.D., 4200 E. 9th Avenue, Denver, Colo.

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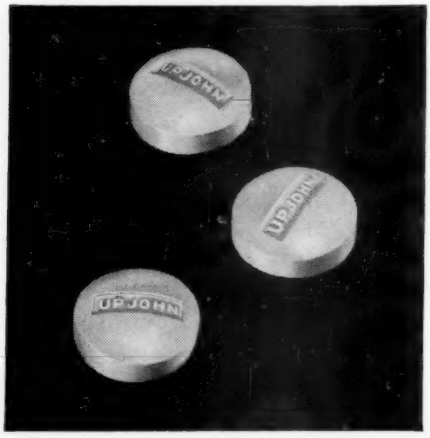

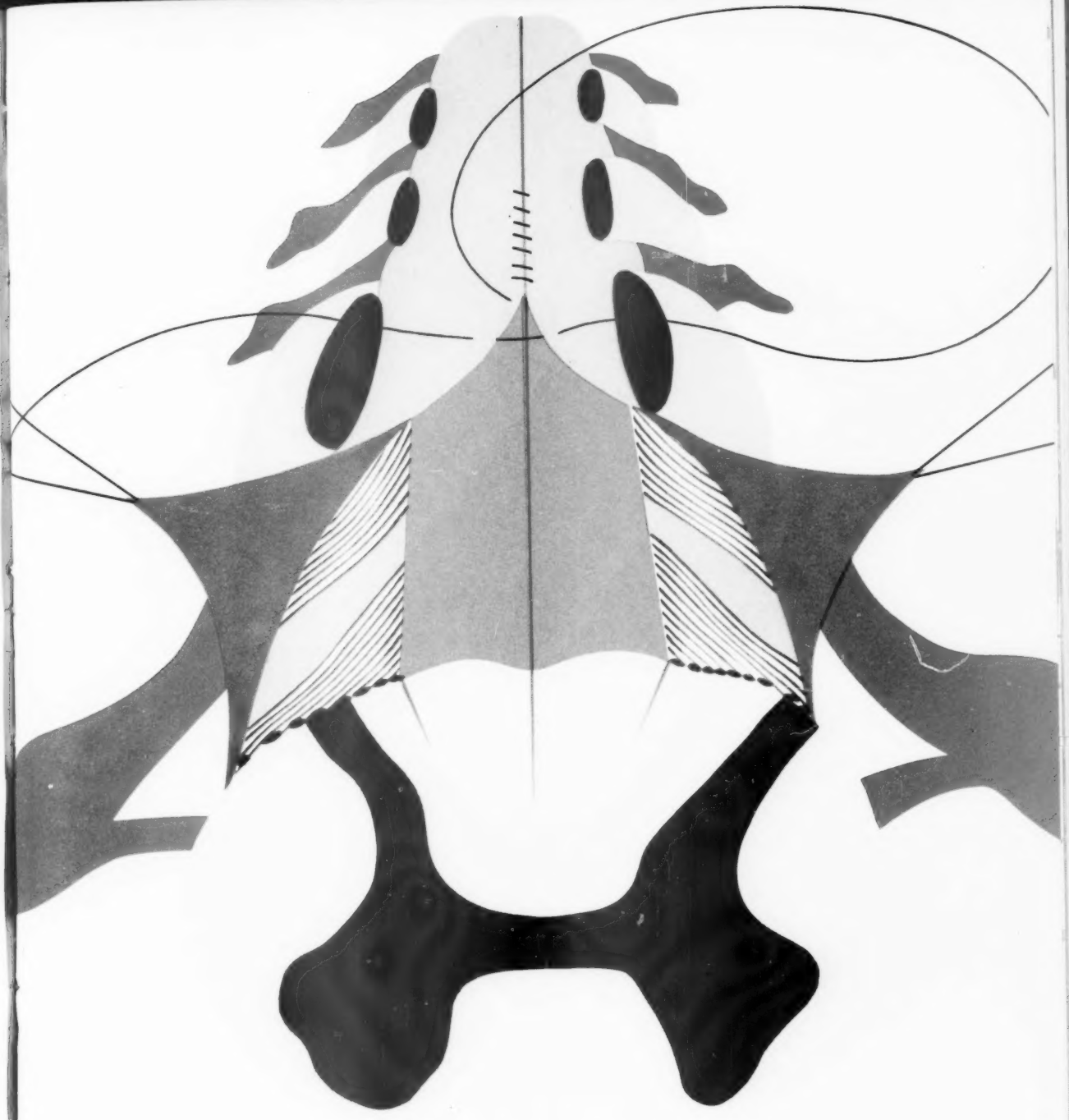

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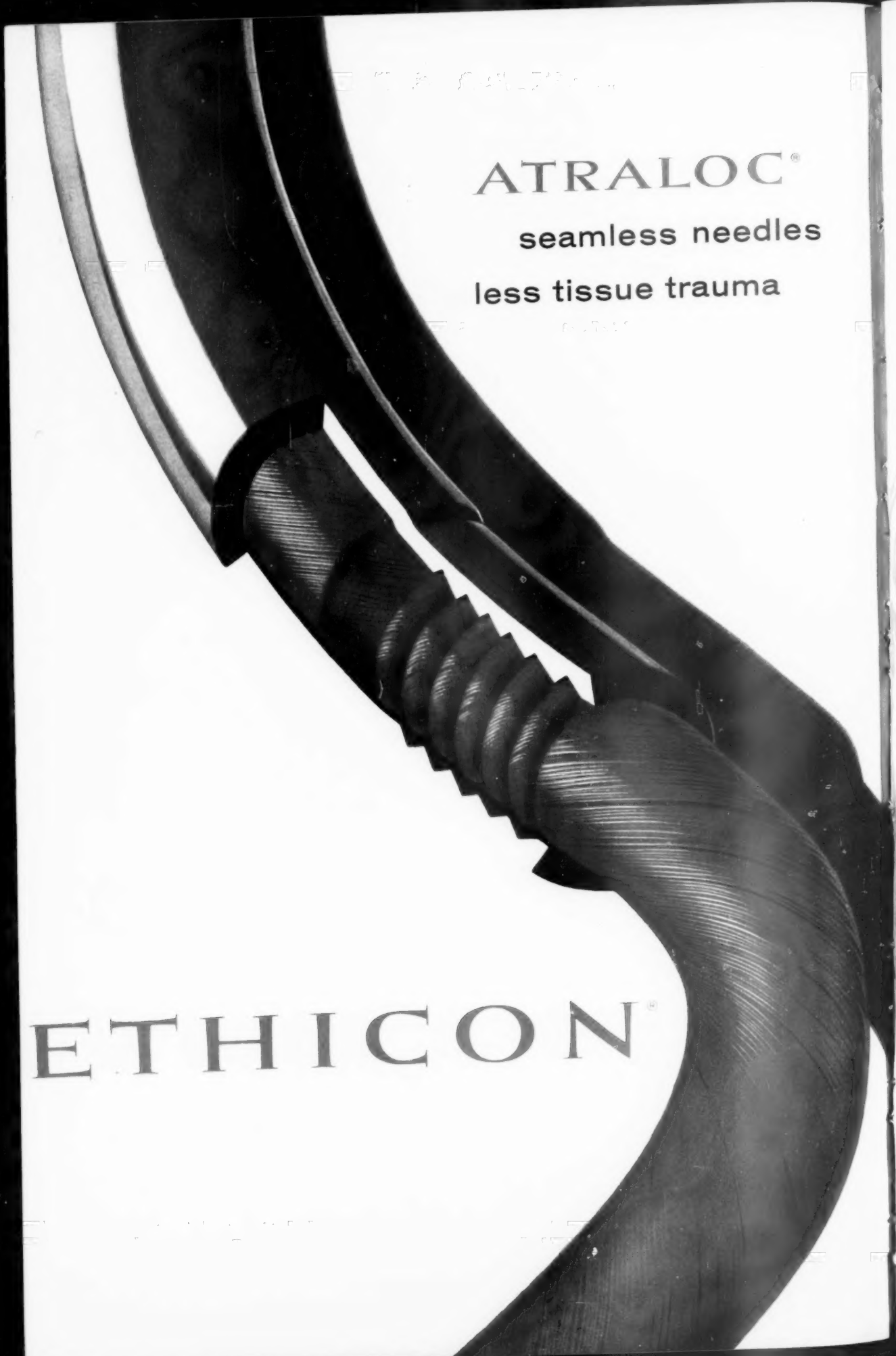
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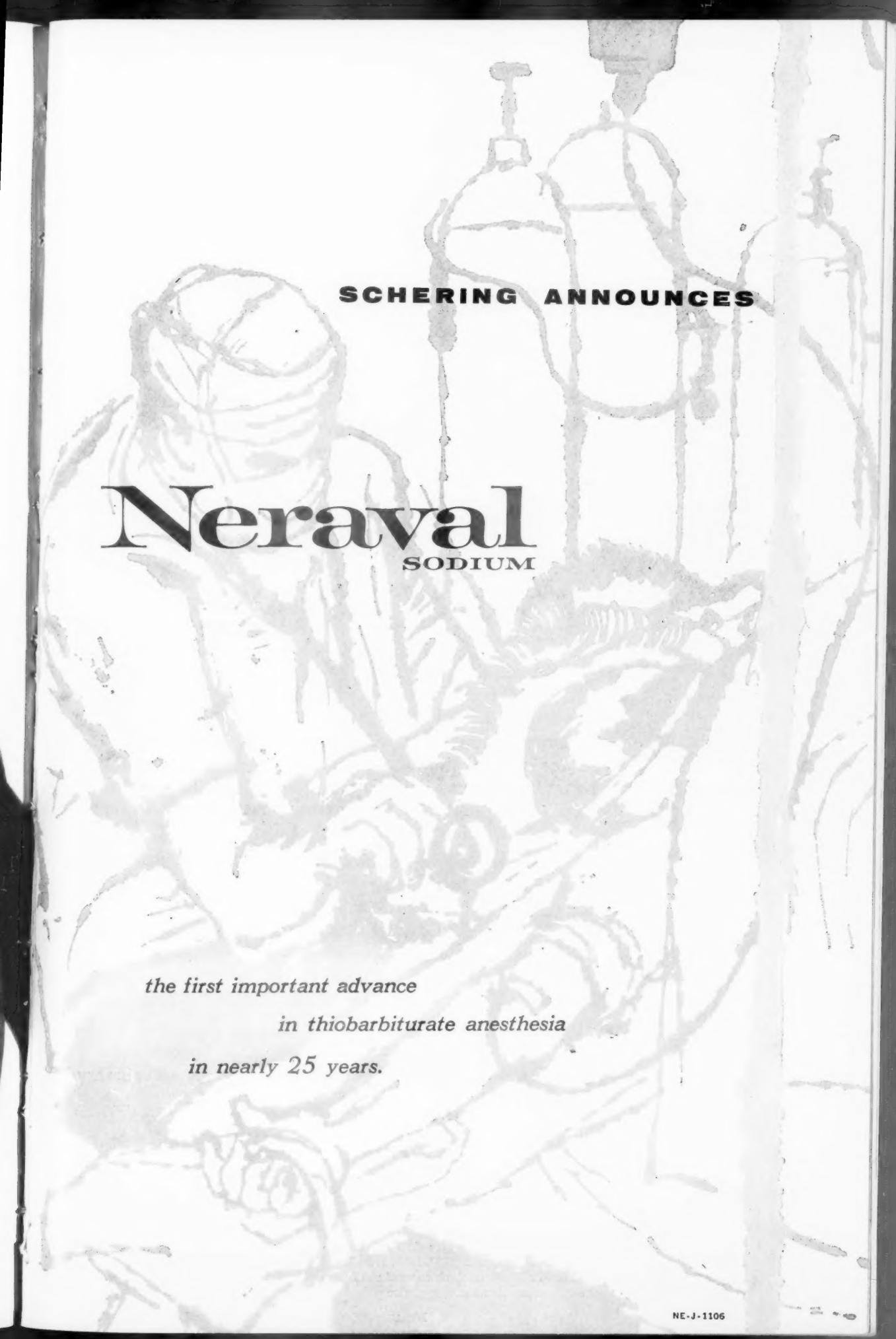

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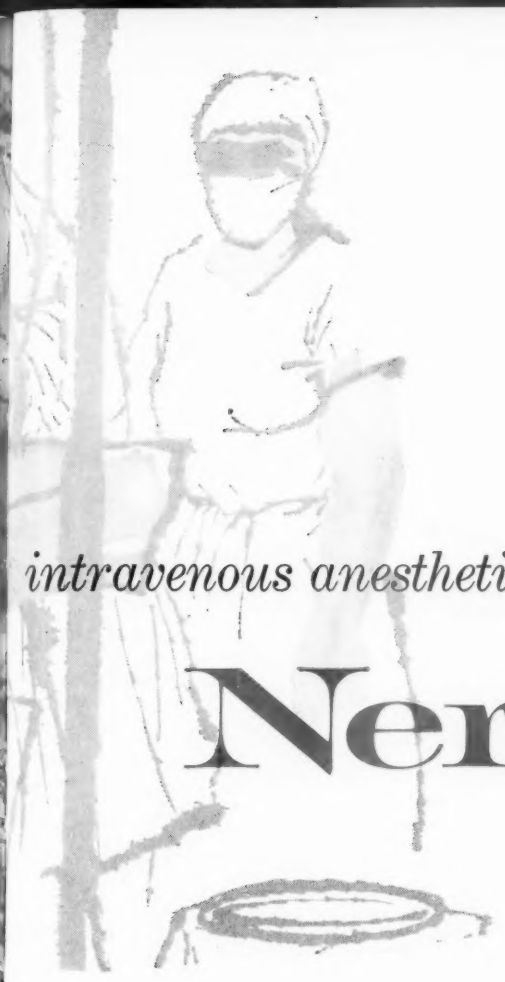

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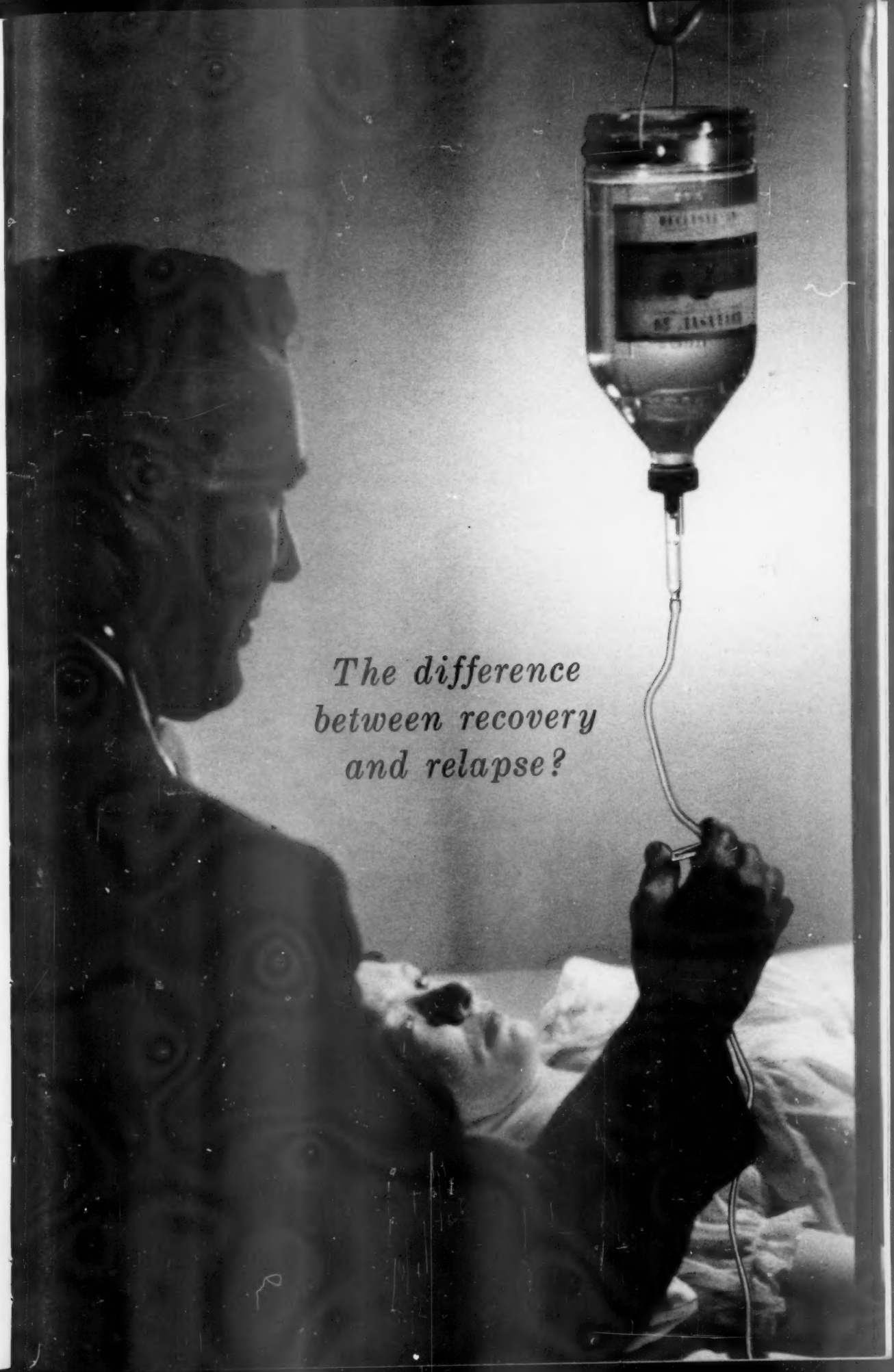
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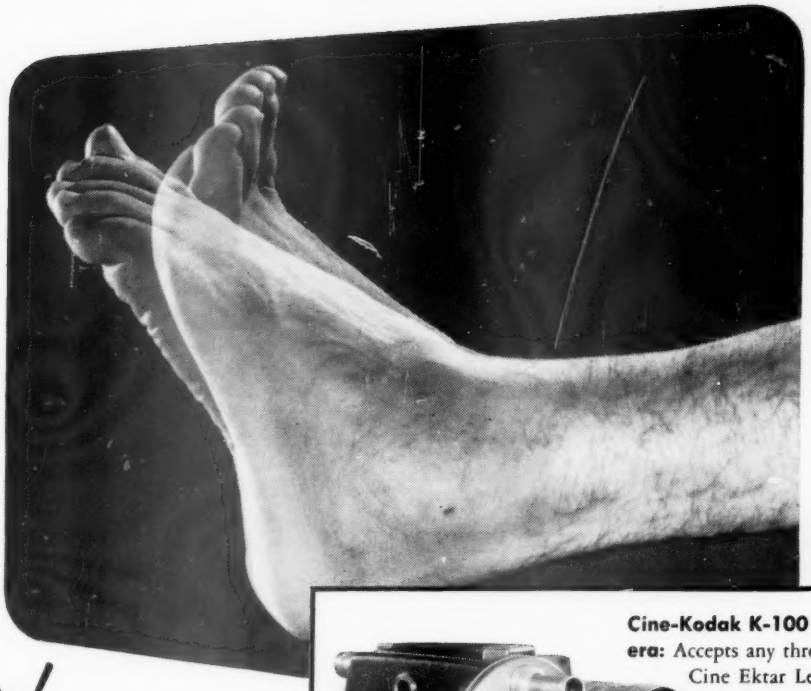

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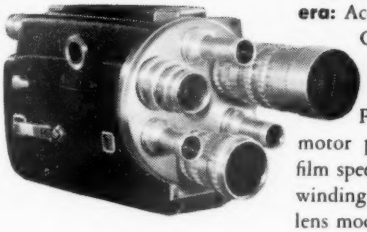

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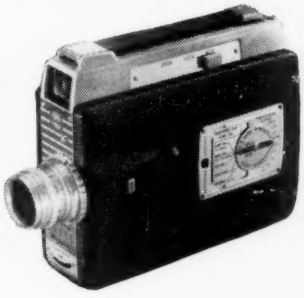

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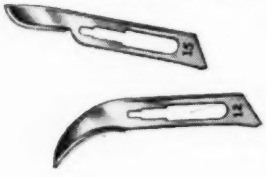

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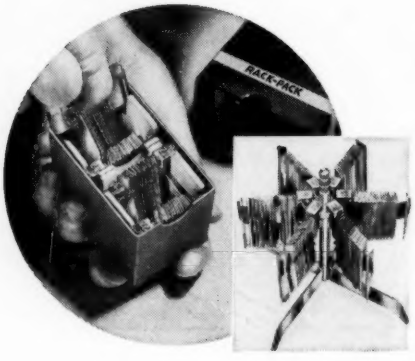

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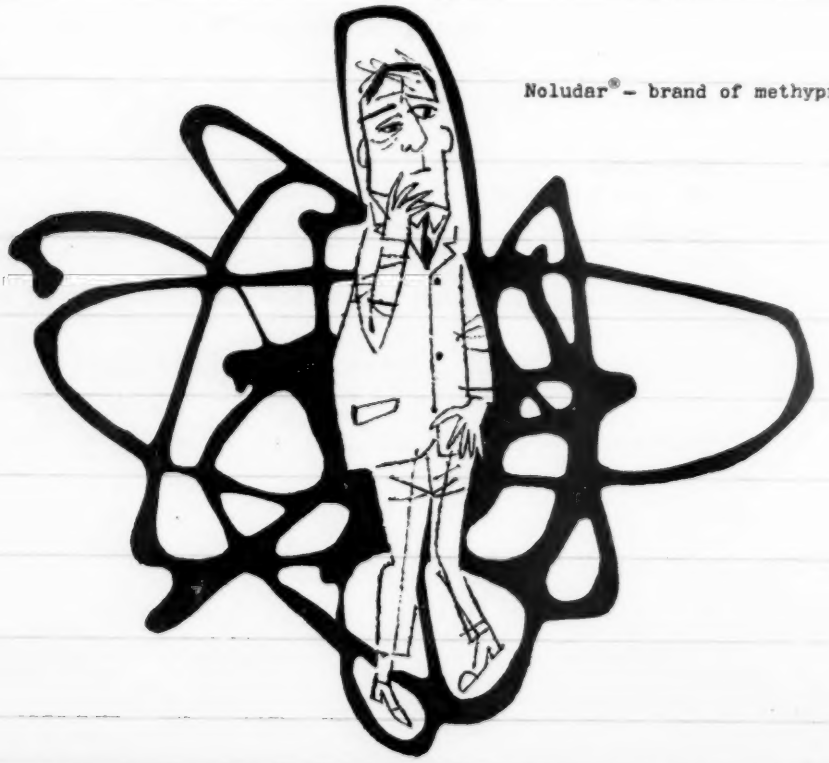

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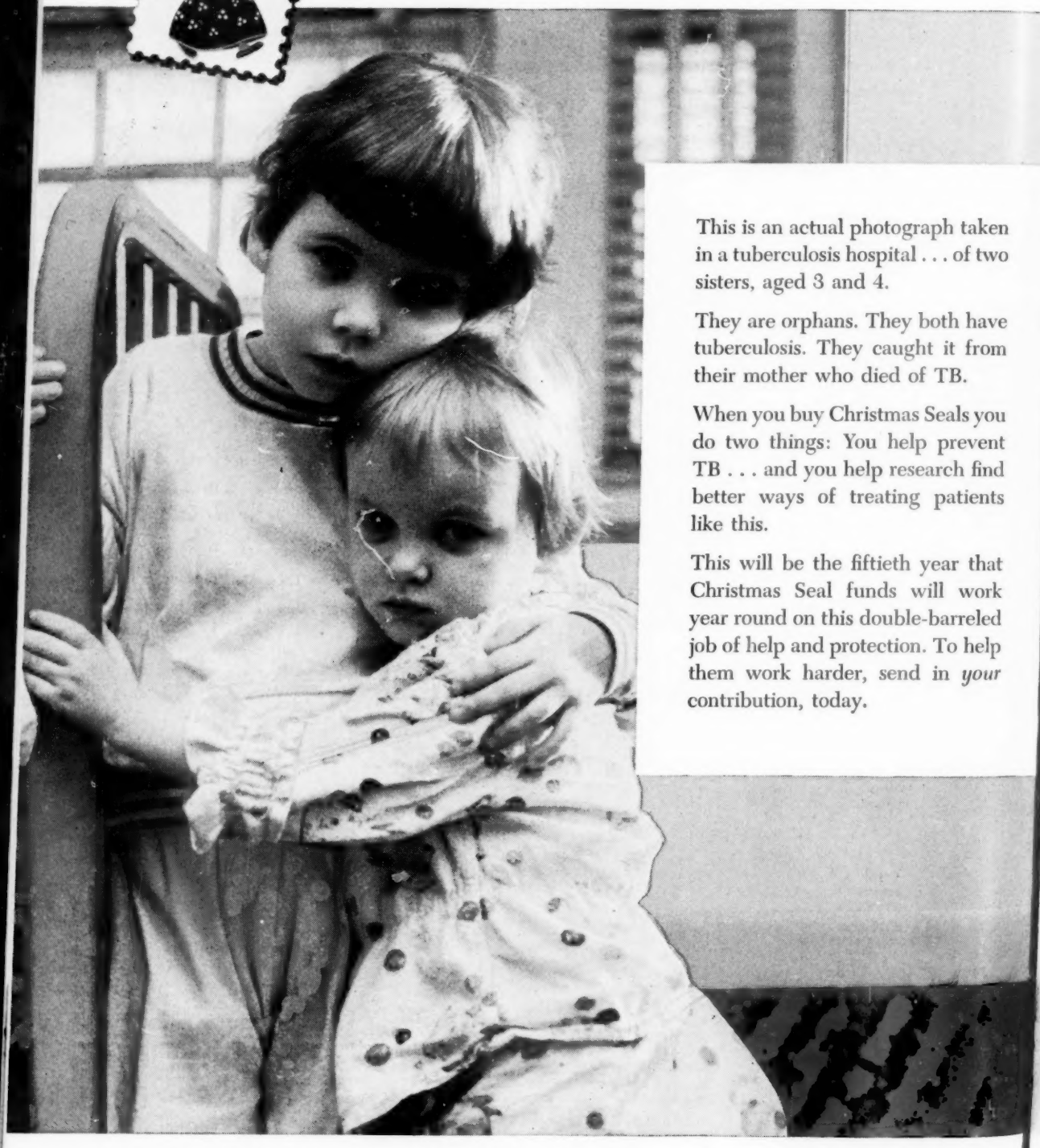

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